Future Research Prioritization Topic Briefs

PCORI Scientific Program Area:
Assessment of Prevention, Diagnosis and Treatment Options

Duke Evidence Synthesis Group, Durham, NC

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Questions or comments may be sent to PCORI at info@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

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Future Research Prioritization: Genetic Testing in Children in Whom a Rare Genetic Disease is Suspected

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ABSTRACT

While the development of affordable and disease-specific genetic tests has greatly aided diagnosis and management of genetic diseases in children, there remains substantial uncertainty as to appropriate use of available diagnostic tests. Despite this uncertainty, utilization of such genetic testing continues to increase. This report outlines the process for engaging a diverse group of stakeholders to develop a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) on the use of genetic testing in children suspected of having a rare genetic disease. Evidence gaps were identified by reviewing existing literature and engaging diverse stakeholders to refine these gaps. Stakeholders ranked evidence gaps by importance from their perspectives using a forced-ranking prioritization method. PubMed was searched for relevant recent studies, and ClinicalTrials.gov was searched for relevant ongoing trials for the highest-ranked evidence gaps. Stakeholders prioritized evidence gaps relating to 4 primary areas of uncertainty: 1) patients' and families' experiences of genetic testing; 2) provider strategies for supporting patients undergoing genetic testing; 3) shared decision-making regarding genetic testing; and 4) patient-centered outcomes for clinical care and research in genetic testing. Our scan of recent and ongoing studies supports this topic as a high-priority area for future research, though a comprehensive systematic review has not been done.

INTRODUCTION

Genetic diseases are disorders that result from alterations in genes, or 'mutations.' These conditions may occur sporadically, but because they result from gene abnormalities, are often inherited.[1,2] Genetic diseases can manifest a wide spectrum of symptoms, ranging in severity from mild to life-threatening or life-limiting.[1,3] Genetic diseases vary in their incidence and prevalence, but are often rare. In part because of this rarity, these disorders can be difficult for many providers to diagnose, which may translate to a long and challenging diagnostic odyssey for patients and families.[1,2,4]

Given that many genetic diseases present during childhood, genetic testing of minors is particularly widespread.[3] Genetic testing in children can be used for many purposes, including screening, diagnosis, predicting the risk of future events, and informing treatment decisions.[1,5,6] As opposed to 'genetic screening,' which describes evaluation on a population basis to identify at-risk individuals, other types of childhood genetic testing are performed when there is suspicion for a genetic disorder based on clinical presentation, family history, ethnicity, or other factors.[3,5]

Early identification of a genetic disease may impact a child's prognosis by facilitating early initiation of preventive monitoring and/or therapeutic interventions.[4] However, for several reasons, appropriate use of available diagnostic tests is often uncertain: 1) genetic tests for many diseases are developed on the basis of limited data related to the condition and may not provide valid or useful results; 2) there are potential emotional and social consequences associated with genetic testing, such as anxiety, depression, and stigmatization; 3) genetic testing may be unable to determine if a child with a given mutation will ever develop symptoms of a disease or how severe any symptoms will be; and 4) many genetic diseases lack treatment options once they are diagnosed.[2,3,6,7] Further, the processes associated with genetic testing in children, including the specific tests utilized, the timing of testing, and the types of medical providers available to guide and inform the testing process, vary widely in different settings.[3,8,9] For these reasons and others, testing children for genetic diseases remains controversial—yet utilization of such genetic testing is increasing.[3,6]

Given the clinical importance of genetic diseases in children, the increasing use of genetic testing despite ongoing uncertainty in many areas, and the variety of potentially relevant patient-centered outcomes, we sought to create a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) that would incorporate different stakeholders' perspectives. For the purposes of this project, we focus mainly on testing intended to facilitate disease diagnosis, risk prediction, and management of rare genetic diseases in children—we do not address genetic screening in infants or other populations.

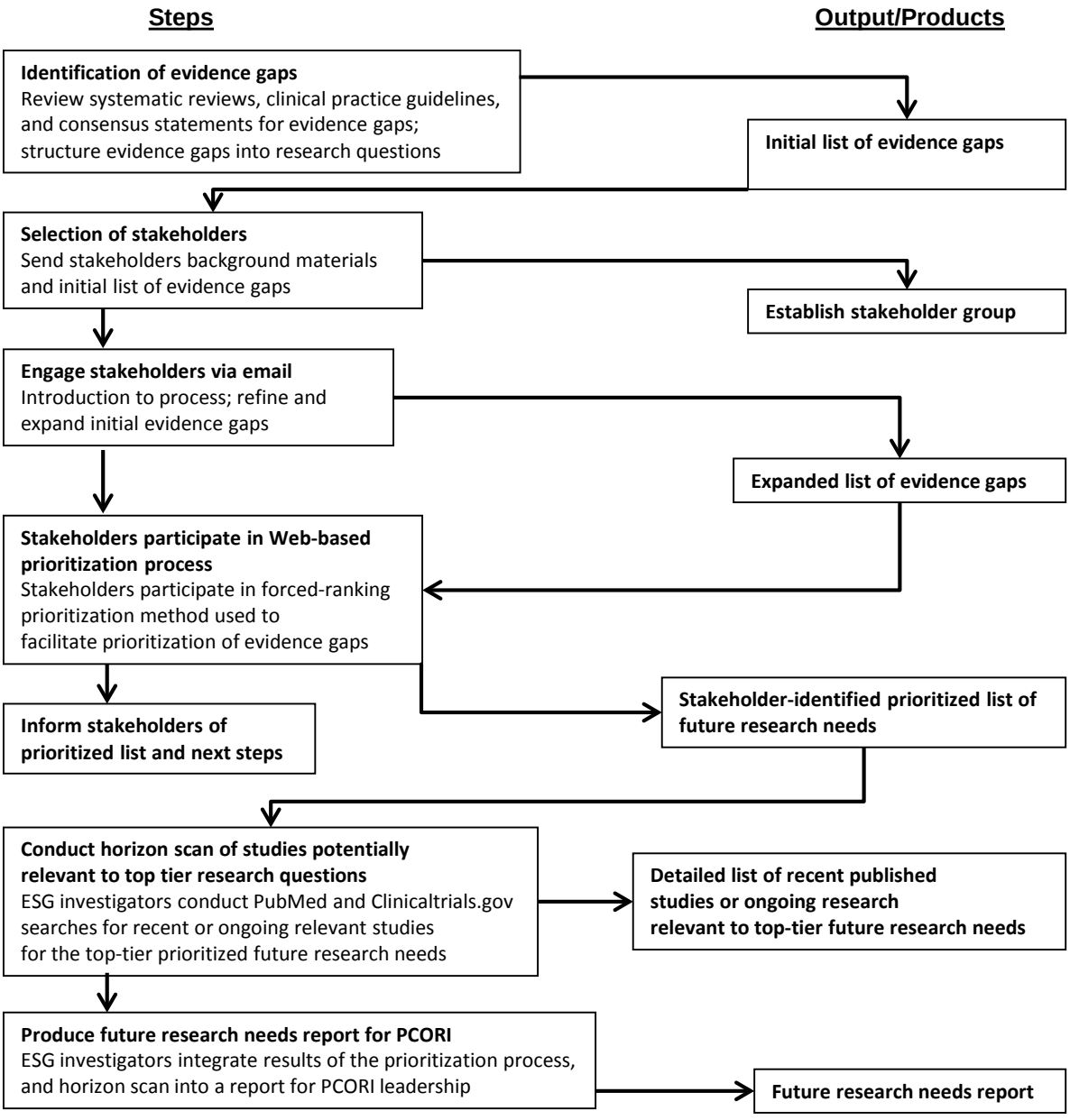
A central goal of PCORI is to engage stakeholders in its work in a meaningful way. Between September 2012 and January 2013, PCORI undertook a broad effort to solicit research topics to consider for targeted funding from patients, caregivers, researchers, and results of previous prioritization processes by groups, such as the Institute of Medicine.[10] In 2014, PCORI's Assessment of Prevention, Diagnosis, and Treatment Options program, together with the program's external advisory panel, identified the use of genetic testing in children in whom a rare disease is suspected as an important topic with unmet research needs. Then, PCORI tasked the Duke University Evidence Synthesis Group (ESG) to work with various stakeholders to identify and prioritize the future research that is most needed by patients and other decision makers on this topic.

METHODS

Overview of Prioritization Approach

Our approach to prioritizing future research and developing recommendations for targeted future funding by PCORI included several steps (Figure 1). These included appraisals of recent systematic reviews to preliminarily identify important evidence gaps, transformation of evidence gaps into research questions, engagement of stakeholders to identify additional gaps and prioritize research needs or questions, and scans of recently published and ongoing studies relevant to the stakeholders' list of prioritized research needs.

Figure 1. Overview of prioritization process


Steps
Output/Products
Identification of evidence gaps
Review systematic reviews, clinical practice guidelines, and consensus statements for evidence gaps; structure evidence gaps into research questions
Initial list of evidence gaps
Selection of stakeholders
Send stakeholders background materials and initial list of evidence gaps
Establish stakeholder group
Engage stakeholders via email
Introduction to process; refine and expand initial evidence gaps
Expanded list of evidence gaps
Stakeholders participate in Web-based prioritization process
Stakeholders participate in forced-ranking prioritization method used to facilitate prioritization of evidence gaps
Inform stakeholders of prioritized list and next steps
Stakeholder-identified prioritized list of future research needs
Conduct horizon scan of studies potentially relevant to top tier research questions
ESG investigators conduct PubMed and Clinicaltrials.gov searches for recent or ongoing relevant studies for the top-tier prioritized future research needs
Detailed list of recent published studies or ongoing research relevant to top-tier future research needs
Produce future research needs report for PCORI
ESG investigators integrate results of the prioritization process, and horizon scan into a report for PCORI leadership
Future research needs report

Identification of Evidence Gaps

We used an iterative process to identify evidence gaps for genetic testing in children in whom a rare disease is suspected. First, we identified and appraised recent published systematic reviews, clinical practice guidelines, and future research needs documents to develop an initial list of evidence gaps which we then transformed into research questions.

Selection and Engagement of Stakeholders

We solicited participation from a group of 30 stakeholders, including clinical experts and researchers in use of genetic testing and pediatrics, representatives from federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision makers and policymakers, and representatives from related consumer and patient advocacy groups (Table 1). Within each of these categories, we sought to identify a person who was either familiar with the clinical areas and their current uncertainties or brought a specific methodological expertise to the stakeholder panel. We solicited and received stakeholder input at various points in the process through email detailing the process and outlining existing evidence gaps, and a Web-based survey to obtain priority ranking of topics.

Table 1. Stakeholder organizations and perspectives

Organization	Stakeholder Perspective	Purpose
Genetics Society of America	Professional societies/researchers	The professional membership organization for scientific researchers and educators in the field of genetics. Our members work to advance knowledge in the basic mechanisms of inheritance, from the molecular to the population level.
American Society of Human Genetics	Professional societies/researchers	The primary professional membership organization for human genetics specialists worldwide. The Society's nearly 8,000 members include researchers, academicians, clinicians, laboratory practice professionals, genetic counselors, nurses and others who have a special interest in the field of human genetics.
American Academy of Pediatrics	Professional societies/researchers	An organization of 62,000 pediatricians committed to the optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.
National Society of Genetic Counselors	Professional societies/researchers	The National Society of Genetic Counselors (NSGC) promotes the professional interests of genetic counselors and provides a network for professional communication. Local and national continuing education opportunities and the discussion of all issues relevant to human genetics and the genetic counseling profession are an integral part of membership in NSGC.
Genetic Alliance	Consumer and patient advocacy	Genetic Alliance is one of the world's leading nonprofit health advocacy organizations. Its network includes more than 1,200 disease-specific advocacy organizations, as well as thousands of universities, private companies, government agencies, and public policy organizations. The network is a dynamic and growing open space for shared resources, creative tools, and innovative programs. Originally founded as an alliance for support groups, Genetic Allian's work has evolved along with the growing health advocacy movement and the rapid advancement of genetic technology.
Coalition for Genetic Fairness (Council for Responsible Genetics)	Consumer and patient advocacy	The Coalition for Genetic Fairness was founded in 1997 to address the growing concern surrounding the misuse of genetic information in health insurance and employment decisions. The founding organizations included the Alpha-1 Association, Genetic Alliance, Hadassah, National Partnership for Women & Families, National Society of Genetic Counselors, and the National Workrights Institute. The Coalition's objective was to educate the public and Congress about genetic discrimination, so introduced genetic nondiscrimination legislation could be seriously considered. Initially, the Coalition consisted of civil rights, disease-specific, and healthcare organizations, but in 2005 the CGF expanded to include industry groups and employers.

Organization	Stakeholder Perspective	Purpose
National Human Genome Research Institute	Healthcare decision- and policy makers	NHGRI supports the development of resources and technology that will accelerate genome research and its application to human health. A critical part of the NHGRI mission continues to be the study of the ethical, legal and social implications (ELSI) of genome research. NHGRI also supports the training of investigators and the dissemination of genome information to the public and to health professionals.
American College of Medical Genetics	Professional societies/researchers	The American College of Medical Genetics and Genomics will: Define and promote excellence in the practice of medical genetics and genomics and the integration of translational research into practice; Promote and provide medical genetics and genomics education; Increase access to medical genetics and genomics services and integrate them into patient care; Advocate for and represent providers of medical genetics and genomics services and their patients; and Maintain structure and integrity of ACMG and its value to members and the public.
Patient Advocate	Patient advocacy	To represent research priorities and issues from the patient's perspective.

Abbreviations not defined above: ACMG=American College of Medical Genetics; CGF=Coalition for Genetic Fairness; NHGRI=National Human Genome Research Institute

Prioritization of Future Research

After expansion of the identified research priorities, stakeholders were invited to rank the revised future research needs online. The survey used a forced-ranking prioritization method described by the Agency for Healthcare Research and Quality Evidence-based Practice Center's Future Research Needs projects,[11] whereby participants were given 6 votes that could be allocated to any identified research priorities, with a maximum of 3 votes per item. The stakeholders were not given specific prioritization criteria to use but rather were told to decide, on the basis of their perspectives, which were the most important unanswered research questions in the use of genetic testing in children in whom a rare disease is suspected. We also asked stakeholder to self-report their perspective understanding that an individual stakeholder could represent more than one perspective. Possible perspectives included: patients and the public, providers, purchasers, payers, policymakers, product makers, and principal investigators. Because our initial set of evidence gaps did not focus on specific genetic tests or diseases, we also asked stakeholders the following question: "Are there specific genetic tests and/or rare genetic diseases in children that you believe would be appropriate 'test cases' to use for further exploration of

potential evidence gaps? (considerations include: conditions with reliable, validated testing options vs. conditions with less reliable options; conditions that are untreatable vs. treatable vs. treatable only with experimental therapies; conditions with severe symptoms vs. less severe symptoms; conditions with shortened lifespan vs. normal lifespan)."

Only the priorities in the top tier (n=9) moved on to the final stage of horizon scan. Stakeholders were informed of the final ranking of future research priorities.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

We performed 2 database searches to identify recently published and ongoing studies relevant to the top-tier future research questions resulting from the stakeholder forced-ranking prioritization exercise. We searched PubMed to identify relevant literature published during the past 5 years and ClinicalTrials.gov for ongoing and recently completed studies. For the search of ClinicalTrials.gov, we used the keywords ("genetic" OR "genome") AND ("screening" OR "test") and focused on children and Phase 3 or 4 studies. Appendix A provides the exact search strategy used for PubMed.

Members of the ESG team reviewed the titles and abstracts identified by searching PubMed for applicability to the top-tier research questions. Articles were included if they met all of the following criteria: presented original data or secondary analysis of data from an RCT, prospective or retrospective observational study, or relevant modeling study; included data related to genetic testing in children for whom certain rare diseases (specified below and in Appendix A) were suspected; and had a stated objective that could be categorized according to our identified list of research priorities.

For the ClinicalTrials.gov search, a member of the ESG team reviewed all study abstracts identified by the search and coded them as potentially relevant to 1 or more of the identified research priorities. We then abstracted study type (such as observational or RCT), recruitment status, and sample size.

RESULTS

Expansion of Evidence Gaps Through Stakeholder Engagement

Of the 30 solicited stakeholders, 9 provided input and helped expand the initial list of 9 evidence gaps to 17. In general, stakeholder input served to identify gaps geared toward understanding and optimizing: 1) patients' and families' experiences of genetic testing; 2) provider strategies for supporting patients undergoing genetic testing; 3) shared decision-making between patients and providers regarding genetic testing; and 4) definition and measurement of patient-centered outcomes pertaining to genetic testing for clinical care and research.

Stakeholder Ranking of Future Research Needs

Table 2 shows the 17 final potential research topics and stakeholder ranking. Thirteen stakeholders completed the prioritization exercise. We also indicate in Table 2 the number of stakeholders who voted for each specific research topic, and the diverse perspectives represented by these votes. Across the 13 stakeholders, 2 self-identified as patients, 12 as providers, 5 as a policy makers, and 5 and principal investigators. No stakeholders self-identified as purchasers, product makers, or payers.

Table 2. Final ranking of future research needs for genetic testing for children in whom a rare disease is suspected

Question	Score	Stakeholders, *n*	Perspectives[§]
Top Tier			
1. What is the value of genetic testing for children in whom a rare disease is suspected (and their caregivers), and how can we best measure this value?*	22	10	2 patients, 10 providers, 5 policy makers, 2 PIs
2. What support tools, training, and resources best enable providers to optimally care for children in whom a rare disease is suspected (and their caregivers)?*	9	7	1 patient, 7 providers, 3 policy makers, 2 PIs
3. What are the most important patient-centered outcomes relating to genetic testing for children in whom a rare disease is suspected (and their caregivers)?	6	5	1 patient, 5 providers, 2 policy makers, 1 PI
4. How does the diagnostic odyssey experienced prior to clinical consultation influence perceptions of genetic testing and testing decisions for children in whom a rare disease is suspected (and their caregivers)?*	5	3	1 patient, 3 providers, 1 policy maker
5. What are the comparative benefits and risks of formal genetic counseling prior to and following genetic testing among children in whom a rare disease is suspected (and their caregivers)?*	5	3	3 providers, 1 PI
6. How can children in whom a rare disease is suspected (and their caregivers) become better prepared to process relevant health and psychosocial information, understand limitations of this information, decide how to act on this information, and stay informed beyond their initial decision?*	4	4	1 patient, 4 providers, 1 policy maker, 3 PIs
7. What strategies are most effective in informing shared decision-making with regard to the benefits and risks of pursuing genetic testing in children in whom a rare disease is suspected (and their caregivers)?	4	4	4 providers, 1 policy maker, 2 PIs
8. How does the composition of the care team (e.g., genetic counselors, medical geneticists or other specialist providers, generalist providers, other clinicians) influence outcomes for children receiving genetic testing (and their caregivers)?*	4	4	4 providers, 1 policy maker, 3 PIs
9. How do shared decision-making processes for genetic testing and patient-centered outcomes differ depending on the types of tests available (e.g., targeted testing for mutations vs. broader approaches like whole-exome or whole-genome sequencing (including the recommendation to analyze and report on the 56 'medically actionable genes')?*	4	4	3 providers, 1 policy maker, 3 PIs

Question	Score	Stakeholders, *n*	Perspectives[§]
Middle Tier			
10. How do shared decision-making processes for genetic testing and patient-centered outcomes differ across conditions (conditions that are untreatable vs. treatable; conditions with severe symptoms vs. less severe symptoms; conditions with shortened lifespan vs. normal lifespan)?*	3	3	1 patient, 2 providers, 1 policy maker, 1 PI
11. What is the utility of different measurement tools and strategies for assessing patient-centered outcomes of genetic testing in comparative effectiveness research and care of children in whom a rare disease is suspected?*	3	1	1 PI
Lower Tier			
12. How can providers best support children in whom a rare disease is suspected (and their caregivers) during and following their diagnostic odyssey (including: receiving negative results requiring continued odyssey; receiving a diagnosis with available treatments; and receiving a diagnosis with no available treatments)?*	2	2	1 patient, 1 provider, 1 policy maker, 1 PI
13. How can providers best communicate the limitations of genetic testing to children in whom a rare disease is suspected (and their caregivers), along with lost opportunities if testing is not pursued?*	2	2	2 providers, 1 PI
14. How can new and emerging genetic risk technologies continually be incorporated into shared decision-making regarding genetic testing in children in whom a rare disease is suspected (and their caregivers)?	2	2	1 patient, 2 providers, 1 policy maker
15. How do providers navigate the risks/benefits and ethical issues of cascade testing of family members after a genetic mutation is discovered (e.g., whom to test, individuals' 'right not to know,' non-paternity, etc.)?*	2	2	2 providers, 1 policy maker, 2 PIs
16. How do providers navigate the risks/benefits and ethical issues of direct-to-consumer advertisement of genetic testing for children in whom a rare disease is suspected (if this is still continuing)?*	1	1	1 provider, 1 PI
17. What types of providers (e.g., genetic counselors, medical geneticists or other specialist providers, generalist providers, other clinicians) currently provide genetic counseling for children in whom a rare disease is suspected (and their caregivers), and how do current counseling practices differ across specialties?*	0	0	–

§ "Perspectives" indicates the self-reported perspectives represented by the stakeholders who voted for the individual evidence gaps. Note that an individual stakeholder could self-identify as representing more than one perspective (i.e., he/she could self-identify as both a patient and a provider); for this reason, the number of perspectives does not necessarily equal the number of stakeholders.

* Indicates evidence gaps that were added or substantially revised by stakeholders.

Abbreviations: *n*=number (of stakeholders); PI(s)=principal investigator(s)

The top 9 future research needs prioritized by stakeholders included evidence gaps representing all 4 of the general categories from the expanded list. There were 3 gaps addressing patients' and families' experiences of genetic testing (gaps 1, 4, and 6 from Table 2); 3 gaps relating to provider strategies for supporting patients undergoing genetic testing (gaps 2, 5, and 8); 2 gaps pertaining to shared decision-making regarding genetic testing (gaps 7 and 9); and 1 gap addressing patient-centered outcomes for genetic testing in clinical care and research (gap 3).

Of note, 7 of the top 9 evidence gaps were topics suggested explicitly by our stakeholder group. Given the initial broad scope of this topic, our process greatly benefited from the initial input from the stakeholder group as reflected by the prioritization process findings.

Note we also asked stakeholders about specific genetic tests or diseases which they would suggest as exemplars for these evidence gaps. Responses suggested using:

- Hereditary cancer syndromes
- Duchenne Muscular Dystrophy
- Autism
- Resistant epilepsy
- Fragile X Syndrome
- Huntington Disease
- Lysosomal storage disorders (including treatable diseases, e.g., Type I Gaucher, vs. less treatable diseases, e.g., Tay Sachs or Type II Gaucher)
- Spinal Muscle Atrophy

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

Our PubMed search identified 893 articles. Of these, 43 met our inclusion criteria and included 8 systematic reviews, 3 RCTs, 29 cohort studies, 0 case–control studies, and 3 of other study designs. Sample sizes ranged from 8 to 31,428. Only 3 studies were active comparator studies, 1 studies either were placebo-controlled or used standard of care as the comparison, and 39 studies had no comparator.

The number of relevant citations varied for the different prioritized research needs. Six of the top 9 prioritized research needs had 10 or more relevant citations. These included prioritized gap 2 (*What support tools, training, and resources best enable providers to optimally care for children in whom a rare disease is suspected?*, n=22), prioritized gap 1 (*What is the value of genetic testing for children in whom a rare disease is suspected, and how can we best measure this value?*, n=17), prioritized gap 7 (*What strategies are most effective in informing shared decision-making with regard to the benefits and risks of pursuing genetic testing in children in whom a rare disease is suspected?*, n=15), prioritized gap 3 (*What are the most important patient-centered outcomes relating to genetic testing for children in whom a rare disease is suspected?* , n=11), and prioritized gaps 5 and 8 (*What are the comparative benefits and risks of formal genetic counseling prior to and following genetic testing among children in whom a rare disease is suspected?* and *How does the composition of the care team influence outcomes for children receiving genetic testing?* , n=10). Two research needs had fewer than 10 relevant citations, prioritized gap 6 (*How can children in whom a rare disease is suspected become better prepared to process relevant health and psychosocial information, understand limitations of this information, decide how to act on this information, and stay informed beyond their initial decision?*, n=9) and prioritized gap 4 (*How does the diagnostic odyssey experienced prior to clinical consultation influence perceptions of genetic testing and testing decisions for children in whom a rare disease is suspected?*, n=4). Only one of the research needs had no identified citations, prioritized gap 9 (*How do shared decision-making processes for genetic testing and patient-centered outcomes differ depending on the types of tests available?*).

Our search of ClinicalTrials.gov yielded 288 studies. Of these, 278 did not appear to meet eligibility based on question of genetic screening for children in whom a rare disease is suspected (looking at intervention, population, and outcomes fields), and another 8 had been withdrawn or terminated prior to study completion. Of the applicable 2 studies, 1 was recruiting and 1 had been completed. We identified only 2 protocols as clearly relevant to the top-tier research questions. These included a recently completed observational study (n=422) exploring the impact of a positive HD test or presence of HD on family members' perceptions of various

outcomes, and an ongoing RCT (n=400) evaluating the impact of a decision guide used together with genetic counseling on communication between mothers undergoing BRCA1/2 testing and their minor-age children. Both protocols had potential relevance to multiple prioritized gaps.

The Tables in Appendix B detail key characteristics of the included PubMed and ClinicalTrials.gov articles separately for each of the top-tier future research needs.

DISCUSSION

This article outlines our process for developing a prioritized research agenda for PCORI as informed by a diverse group of stakeholders pertaining to the use of genetic testing in children in whom a rare disease is suspected. We developed a list of 17 potential future research topics designed to inform the process of genetic testing in children on the basis of the existing literature and with input from stakeholders. The stakeholders prioritized these topics through a forced-ranking process. We then examined recently published and ongoing studies to identify research relevant to the top 9 future research priorities to assist PCORI in developing future targeted funding opportunities. Our stakeholders prioritized evidence gaps that, if addressed, could help inform 4 main areas of uncertainty relating to genetic testing in children.

The first area of uncertainty relates to patients' and families' experiences of genetic testing. The 3 gaps in this area highlight how, given the rarity of many genetic conditions and the variability of testing approaches, seeking a genetic diagnosis can be profoundly challenging for patients and families.[1,2] Our stakeholders felt that highest priority should be given to research designed to enhance our understanding of the value of genetic testing for children and families, as well as how to measure that value (prioritized gap 1). New research in this domain could facilitate the development of genetic testing approaches that maximize value for patients, and also enhance ascertainment of different approaches' comparative impact. Evaluating how the oft-prolonged diagnostic odyssey experienced by patients and families affects their perceptions and decision making (prioritized gap 4) could likewise inform the development of patient-centered approaches to genetic testing, as

would examining how patients process, understand and act upon information from genetic tests (prioritized gap 6).

The second area of uncertainty relates to provider strategies for supporting patients as they undergo genetic testing. Although up to 60% of primary care physicians have ordered genetic tests, literature suggests that half of all primary care physicians lack confidence in their knowledge of genetic testing.[12,13] As utilization of genetic tests continues to increase, it will be essential to assure that ordering providers have the appropriate tools, training, and resources to optimally care for children and their families (prioritized gap 2). To this end, it will also be crucial to evaluate how the extent and timing of formal counseling by trained genetic counselors (prioritized gap 5), as well as the composition of care teams (prioritized gap 8) influence patient-centered outcomes.

The third area of uncertainty relates to shared decision making for genetic testing. Shared decision making refers to a process by which patients and providers together consider outcome probabilities and patient preferences and reach health care decisions based on mutual agreement; this approach is well-suited for problems like genetic testing that involve uncertainty.[14] Our stakeholders felt that research designed to inform strategies for shared decision making regarding the benefits and risks of genetic testing could improve patient-centered outcomes (prioritized gap 7). Further, because the specific tests available for a genetic disease likely impact shared decision-making processes, stakeholders felt exploration of this area would be important (prioritized gap 9); of note, this was the only evidence gap for which we were unable to find any recent or ongoing studies.

The fourth and last area of uncertainty relates to patient-centered outcomes for genetic testing in clinical care and research (prioritized gap 3). Improving outcomes through patient-centered comparative clinical effectiveness research is central to PCORI's mission;[15] because the most relevant patient-centered outcomes pertaining to genetic testing in children remain uncertain, addressing this evidence gap will be integral to improving patient-centered outcomes through clinical care and research.

Our horizon scan highlights the relative paucity of recent and ongoing research in the areas of uncertainty prioritized by our stakeholders, and supports these evidence gaps as important targets for new research. Insufficient evidence is likely a major factor affecting patient and family decision making regarding genetic testing, and likely also impacts providers' ability to serve as an optimal resource for children and their families. Although genetic testing in children was not identified by the Institute of Medicine as a priority area in their 2009 list of 100 priorities for comparative effectiveness research,[10] the clinical impact of genetic diseases and the increasing utilization of genetic testing argue for the importance of patient-centered outcomes research in this domain.

One final factor in considering future research in the area of genetic testing is that best practices may vary based on the genetic disease in question. Symptom burden, life expectancy, and the types of testing available (e.g., targeted testing for mutations vs. broader approaches like whole-exome or whole-genome sequencing) all likely impact patient experiences, provider care, shared decision-making, and patient-centered outcomes. For this reason, we asked our stakeholders to suggest example diseases that could make good initial candidates for patient-centered research. Options suggested by our stakeholders included Duchenne Muscular Dystrophy, Fragile X Syndrome, lysosomal storage disorders, Huntington Disease, and others. Although future research should certainly not be limited to these diseases, this list may represent a reasonable starting point.

Our prioritization process is not without limitations. Although we took efforts to be comprehensive, it is possible that the list of future research needs we generated and expanded with stakeholder feedback does not reflect the full range of possible future research. In addition, we engaged a relatively small number of stakeholders. It is also possible that another group of stakeholders might rank future research needs differently. Still, we included a diverse stakeholder panel with a range of expertise in determining these priorities with a particular focus on patient-centered research. Also, because a comprehensive systematic review has not been done for many of the identified evidence gaps, we cannot determine with certainty the degree to which prioritized future research needs have already been addressed.

In summary, we engaged a diverse stakeholder group to develop a prioritized research agenda pertaining to the use of genetic testing in children suspected of having a genetic disease. Our stakeholders prioritized evidence gaps relating to 4 primary areas of uncertainty: 1) patients' and families' experiences of genetic testing; 2) provider strategies for supporting patients undergoing genetic testing; 3) shared decision-making regarding genetic testing; and 4) patient-centered outcomes for clinical care and research in genetic testing. We also conducted a horizon scan of recent and ongoing studies, which further supports genetic testing in children as a high-priority topic for future patient-centered outcomes research.

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Appendix A. Pub Med Search Strategy

Search date: January 2, 2015

Set #	Terms	
#1	"Autistic Disorder"[MeSH] OR "Muscular Dystrophy, Duchenne"[MeSH] OR "Epilepsy"[MeSH] "Fragile X Syndrome"[MeSH] OR "Huntington Disease"[MeSH] OR "Lysosomal Storage Diseases"[MeSH] OR "Gaucher Disease"[MeSH] OR "Tay-Sachs Disease"[MeSH] OR "Tay-Sachs Disease, AB Variant"[MeSH] OR "Muscular Atrophy, Spinal"[MeSH] OR "autistic"[tiab] OR "autism"[tiab] OR "duchenne muscular dystrophy"[tiab] OR "epilepsy"[tiab] OR "Fragile X"[tiab] OR "huntington"[tiab] OR "gaucher"[tiab] OR "tay sachs"[tiab] OR "spinal muscle atrophy"[tiab] OR "spinal muscular atrophy"[tiab] OR "Genes, BRCA1"[MeSH] OR "Genes, BRCA2"[MeSH] OR "BRCA1 Protein"[MeSH] OR "BRCA2 Protein"[MeSH] OR "Hereditary Breast and Ovarian Cancer Syndrome"[MeSH] OR "Li-Fraumeni Syndrome"[MeSH] OR "Genes, p53"[MeSH] OR "Hamartoma Syndrome, Multiple"[MeSH] OR "Colorectal Neoplasms, Hereditary Nonpolyposis"[MeSH] OR "Adenomatous Polyposis Coli"[MeSH] OR "Retinoblastoma"[MeSH] OR "Multiple Endocrine Neoplasia Type 1"[MeSH] OR "Multiple Endocrine Neoplasia Type 2a"[MeSH] OR "Multiple Endocrine Neoplasia Type 2b"[MeSH] OR "von Hippel-Lindau Disease"[MeSH] OR "li-fraumeni syndrome"[tiab] OR "cowden syndrome"[tiab] OR "lynch syndrome"[tiab] OR "familial adenomatous polyposis"[tiab] OR "retinoblastoma"[tiab] OR "wermer syndrome"[tiab] OR "multiple endocrine neoplasia"[tiab] OR "von hippel lindau syndrome"[tiab] OR "brca1"[tiab] OR "brca2"[tiab] OR "tp53"[tiab] OR "pten"[tiab] OR "msh2"[tiab] OR "mlh1"[tiab] OR "msh6"[tiab] OR "pms2"[tiab] OR "epcam"[tiab] OR "apc"[tiab] OR "rb1"[tiab] OR "men1"[tiab] OR "ret"[tiab] OR "vhl"[tiab]	241,761
#2	"Diagnosis"[Mesh] OR "diagnosis"[sh] OR "diagnosis"[tiab] OR "diagnostic"[tiab] OR "diagnosing"[tiab] OR "diagnosed"[tiab] OR "diagnose"[tiab]	8,857,365
#3	("Genetic Testing"[Mesh] OR "genetic testing"[tiab] OR "genetic test"[tiab] OR "genetic tests"[tiab] OR "genomic testing"[tiab] OR "genomic test"[tiab] OR "genomic tests"[tiab] OR "genetic screening"[tiab] OR "genomic screening"[tiab] OR "testing"[tiab] OR "screening"[tiab]) NOT ("Prenatal Diagnosis"[MeSH] OR "prenatal"[tiab])	679,056
#4	"Infant, Newborn"[MeSH] OR "Infant"[MeSH] OR "Child"[MeSH] OR "Child, Preschool"[MeSH] OR "Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Young Adult"[Mesh] OR infant[tiab] OR child[tiab] OR children[tiab] OR pediatric[tiab] OR adolescents[tiab] OR adolescent[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR youth[tiab] OR kid[tiab] OR kids[tiab]	3,312,527

Set #	Terms	
#5	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials "[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) OR (("Decision Support Techniques"[Mesh] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab]) AND ("2000"[Date - Publication] : "3000"[Date - Publication])) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4,827,779
	#1 AND #2 AND #3 AND #4 AND #5	2092
	Limits: English, Date: past 5 years	893

Appendix B. Supplementary Tables

Appendix Table B-1. Published and ongoing studies potentially relevant to Research Question 1

[What is the value of genetic testing for children in whom a rare disease is suspected (and their caregivers), and how can we best measure this value?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Sie, 2013[2]	219 patients	This retrospective study evaluates whether the testing age should be above 25 years to prevent adverse effects such as regret or decisional conflict, by determining the percentage and characteristics of patients reporting these problems.
Aktan-Collan, 2013[3]	208 patients	We evaluated long-term psychosocial consequences of predictive genetic testing, and surveillance behaviour in Lynch syndrome (LS).
Krukenberg, 2013[4]	141 patients	Predictive testing for Huntington disease (HD) has been available in the United States (US) since 1987, and the Indiana University Predictive Testing Program has been providing this testing since 1990. To date there has been no published description of those who present for such testing in the US. Here we describe demographics of 141 individuals and reproductive decision making of a subset of 16 of those individuals who underwent predictive HD testing between 1990 and 2010 at one site in the US.
Mand, 2013[5]	9 patients	For the first time, this study reports empirical evidence concerning the process and impacts of predictive testing in mature minors for adult-onset conditions where no medical benefit exists.
Tercyak, 2013[6]	221 patients	Although BRCA1/2 genetic testing is discouraged in minors, mothers may disclose their own results to their children. Factors affecting patients' disclosure decisions and patient outcomes of disclosure are largely unknown.
Wakefield, 2013[7]	1812 patients	NR
Archibald, 2013[8]	188 patients	This project explored, the views of key stakeholders regarding population-based genetic carrier screening for fragile X syndrome (FXS).
Visootsak, 2012[9]	10 patients	NR
May, 2012[10]	NR	The purpose of this study was to solicit the perspectives of parents who have children with autism about screening for genes associated with aggression, compared to responses from those who have children without disabilities and those planning to have children.
Morrison, 2011[11]	212 patients	Using the Northern Ireland Huntington disease (HD) register, the number of prospectively recorded predictive tests was analysed over a 20-year period.

Study	N	Objective
Coulter, 2011[12]	1792 patients	We conducted a retrospective chart review of CMA testing performed during a 12-month period on patients with DD/ID, ASD, and congenital anomalies to determine the proportion of cases where abnormal CMA results impacted recommendations for clinical action.
Gjone, 2011[13]	8 patients	A nationwide sample (n = 22) of adolescent FAP offspring including 85% of eligible individuals aged 11-20 years and their parents were interviewed with regard to adolescent mental health, psychosocial functioning, knowledge about FAP and genetic risk, and experiences with testing and surgery.
Williams, 2010[14]	433 patients	The aim of this study was to examine benefits reported by people with an HD family history or those who have undergone predictive HD testing, as well as the personal variables associated with perceived benefits.
Baer, 2010[15]	31,428 patients	To examine the distribution of familial cancer risk and its associations with genetic testing in the United States.
Duncan, 2010[16]	10 patients	In this paper we present findings from ten in-depth interviews with young people who have undergone predictive genetic testing for FAP (four male, six female; five gene-positive, five gene-negative; aged 10-17 years at the time of their predictive test; aged 12-25 years at the time of their research interview). We present five themes that emerged from the interviews which highlight key ethical challenges associated with such testing.
Rasmussen, 2010[17]	109 patients	To explore the benefits and risks of genetic testing in vHL, including among minors.
Case-Control Studies		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Family Health After Predictive Huntington Disease (HD) Testing (NCT00075140)	422 patients	Completed (October 2008). The purpose of this study is to identify health management concerns and needs of family members of asymptomatic and symptomatic persons with mutation in the gene for Huntington Disease (HD).
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: ASD=autism spectrum disorders; CMA=chromosomal microarray; DD=developmental delay; FAP=familial adenomatous polyposis; HD=Huntington disease; ID=intellectual disability; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; vHL=von Hippel-Lindau disease

Appendix Table B-2. Published and ongoing studies potentially relevant to Research Question 2

[*What support tools, training, and resources best enable providers to optimally care for children in whom a rare disease is suspected (and their caregivers)?]*

Study	N	Objective

Study	N	Objective
Systematic Reviews		
Kamihara, 2014[18]	NR	This review discusses LFS, describes its association with TP53, and examines the classic and evolving definitions of the syndrome. The potential implications of multigene assessments of individuals at increased cancer risk, which have already begun to identify those with very little personal or family cancer history carrying germline TP53 mutations, are considered.
Kusano, 2014[19]	NR	To describe experience screening dialysis patients for Fabry disease
Van der Tol, 2014[20]	51 studies	A systematic review on FD screening studies was performed to interpret the significance of GLA gene variants and to calculate the prevalence of definite classical and uncertain cases.
Heil, 2013[21]	NR	This review aims to provide an overview of autism genetics for the practicing physician and gives hands-on advice on how to follow-up on abnormal CMA findings in individuals with neuropsychiatric disorders.
Walsh, 2011[22]	7 studies	A systematic literature review and meta-analysis were performed to determine the prevalence of these variants among individuals diagnosed with autism spectrum disorders.
Waguespack, 2010[23]	NR	To review childhood pheochromocytoma/paraganglioma, including conditions causing genetic predisposition; role of genetic screening discussed.
Pradhan, 2010[24]	NR	This paper investigates the results of RB1 testing in retinoblastoma management in a tertiary referral centre.
RCTs		
None	–	–
Cohort Studies		
Chong, 2014[25]	105 patients	In this study, we applied oligonucleotide array comparative genomic hybridization as the molecular genetic test in a Chinese cohort of children with DD/ID, autism or MCA.
Kishnani, 2013[26]	647 patients	The diagnostic gap (the time from the onset of symptoms to the diagnosis of Pompe disease) and factors associated with diagnostic delays were examined among Pompe Registry patients in three onset categories: Group A, onset age with cardiomyopathy; Group B, onset 12 months to 12 years.
Howell, 2013[27]	215 patients	Although recent studies have identified pathogenic CNVs in intellectual disability, autism and epilepsy, the utility of CMA testing in a broader cohort of children with neurologic disorders has not been reported.
Fresneau, 2013[28]	20 patients	In 2001, a French expert panel recommended that presymptomatic tests should not be carried out on minors in families affected by Li-Fraumeni syndrome (LFS), flying in the face of possible parental demands for such testing. We decided to investigate the legitimacy of such a recommendation. We aimed to (1) determine the extent to which these doctors were confronted with parental requests for TP53 testing, (2) study how they responded to these requests and the arguments used and (3) assess the attitude of oncogeneticists concerning the normative framework regulating the prescription of tests for minors.

Study	N	Objective
Koutsis, 2013[29]	76 patients	In a cohort of patients with suspected juvenile-onset Huntington disease (HD), we compared HD expansion-positive and -negative cases in order to identify parameters that may allow differentiating between them and may act as a guide to clinicians contemplating genetic testing.
Wakefield, 2013[7]	1812 patients	NR
Visootsak, 2012[9]	10 patients	NR
, 2012[30]	NR	We describe a project aimed at studying a large number of individuals (>200) with specific recurrent genetic variations (deletion or duplication of segment 16p11.2) that increase the risk of developing autism spectrum (ASD) and other developmental disorders.
Mikhail, 2011[31]	8 patients	Here we present eight patients in a cohort of approximately 1,200 patients referred for clinical array CGH testing for various neurodevelopmental phenotypes, who were identified to carry small (<1.0Mb with the majority <500 kb) either total gene or intragenic deletions encompassing critical synaptic and other neurodevelopmental genes.
Coulter, 2011[12]	1792 patients	We conducted a retrospective chart review of CMA testing performed during a 12-month period on patients with DD/ID, ASD, and congenital anomalies to determine the proportion of cases where abnormal CMA results impacted recommendations for clinical action.
Schaefer, 2010[32]	89 patients	The objective of this study was to determine the diagnostic yield in array comparative genomic hybridization for autism at the University of Nebraska Medical Center.
Baer, 2010[15]	31,428 patients	To examine the distribution of familial cancer risk and its associations with genetic testing in the United States.
Shen, 2010[33]	852 patients	Guidelines for chromosomal microarray analysis for autism-spectrum disorders have not been established - paper compares different approaches to genetic testing in autism-spectrum disorders.
Case-Control Studies		
None	–	–
Guideline/Conference Proceeding		
Review/Conference Proceeding Coury, 2015[34]	NA	This article summarizes the proceedings of the Autism Speaks conference on Treating the Whole Person with Autism: Care across the Lifespan. The conference was organized with the intent of providing a forum for both families and professionals to learn about the most current research in the field.
Clinical Guideline Schaefer, 2013[35]	NA	The guidelines in this paper have been developed to assist the clinician in the consideration of these factors.
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: ASD=autism spectrum disorders; CGH=comparative genetic hybridization; CMA=chromosomal microarray; CNVs=copy number variants; DD=developmental delay; FD=Fabry disease; GLA=alpha-galactosidase A; ID=intellectual disability; LFS=Li-Fraumeni syndrome; MCA=multiple congenital anomalies; N=number of studies/patients; NA=not applicable; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-3. Published and ongoing studies potentially relevant to Research Question 3
[What are the most important patient-centered outcomes relating to genetic testing for children in whom a rare disease is suspected (and their caregivers)?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Sie, 2013[2]	219 patients	This retrospective study evaluates whether the testing age should be above 25 years to prevent adverse effects such as regret or decisional conflict, by determining the percentage and characteristics of patients reporting these problems.
Aktan-Collan, 2013[3]	208 patients	We evaluated long-term psychosocial consequences of predictive genetic testing, and surveillance behaviour in Lynch syndrome (LS).
Mand, 2013[5]	9 patients	For the first time, this study reports empirical evidence concerning the process and impacts of predictive testing in mature minors for adult-onset conditions where no medical benefit exists.
Tercyak, 2013[6]	221 patients	Although BRCA1/2 genetic testing is discouraged in minors, mothers may disclose their own results to their children. Factors affecting patients' disclosure decisions and patient outcomes of disclosure are largely unknown.
Archibald, 2013[8]	188 patients	This project explored, the views of key stakeholders regarding population-based genetic carrier screening for fragile X syndrome (FXS).
Visootsak, 2012[9]	10 patients	NR
May, 2012[10]	NR	The purpose of this study was to solicit the perspectives of parents who have children with autism about screening for genes associated with aggression, compared to responses from those who have children without disabilities and those planning to have children.
Williams, 2010[14]	433 patients	The aim of this study was to examine benefits reported by people with an HD family history or those who have undergone predictive HD testing, as well as the personal variables associated with perceived benefits.
Duncan, 2010[16]	10 patients	In this paper we present findings from ten in-depth interviews with young people who have undergone predictive genetic testing for FAP (four male, six female; five gene-positive, five gene-negative; aged 10-17 years at the time of their predictive test; aged 12-25 years at the time of their research interview). We present five themes that emerged from the interviews which highlight key ethical challenges associated with such testing.
Case-Control Studies		
None	–	–
Guideline/Conference Proceeding		

Study	N	Objective
Conference Proceedings Berry-Kravis, 2013[36]	NA	One major obstacle to the demonstration of efficacy in human trials has been the lack of generally accepted endpoints to assess improvement in function in individuals with FXS. To address this problem, the National Institutes of Health convened a meeting of leading scientists and clinicians with the goal of identifying and standardizing outcome measures for use as potential endpoints in clinical trials in FXS.
Ongoing Studies (ClinicalTrials.gov)		
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: HD=Huntington disease; FAP=familial adenomatous polyposis; FXS=fragile X syndrome; N=number of studies/patients; NA=not applicable; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-4. Published and ongoing studies potentially relevant to Research Question 4

[How does the diagnostic odyssey experienced prior to clinical consultation influence perceptions of genetic testing and testing decisions for children in whom a rare disease is suspected (and their caregivers)?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Kishnani, 2013[26]	647 patients	The diagnostic gap (the time from the onset of symptoms to the diagnosis of Pompe disease) and factors associated with diagnostic delays were examined among Pompe Registry patients in three onset categories: Group A, onset age with cardiomyopathy; Group B, onset 12 months to 12 years.
Mand, 2013[5]	9 patients	For the first time, this study reports empirical evidence concerning the process and impacts of predictive testing in mature minors for adult-onset conditions where no medical benefit exists.
Gjone, 2011[13]	8 patients	A nationwide sample (n = 22) of adolescent FAP offspring including 85% of eligible individuals aged 11-20 years and their parents were interviewed with regard to adolescent mental health, psychosocial functioning, knowledge about FAP and genetic risk, and experiences with testing and surgery.
Case-Control Studies		
None	–	–

Study	N	Objective
Ongoing Studies (ClinicalTrials.gov)		
Family Health After Predictive Huntington Disease (HD) Testing (NCT00075140)	422 patients	Completed (October 2008). The purpose of this study is to identify health management concerns and needs of family members of asymptomatic and symptomatic persons with mutation in the gene for Huntington Disease (HD).

Abbreviations not defined above: FAP=familial adenomatous polyposis; N=number of studies/patients; RCTs=randomized controlled trials

Appendix Table B-5. Published and ongoing studies potentially relevant to Research Question 5

[What are the comparative benefits and risks of formal genetic counseling prior to and following genetic testing among children in whom a rare disease is suspected (and their caregivers)?]

Study	N	Objective
Systematic Reviews		
Moeschler, 2014[37]	NR	Global developmental delay and intellectual disability are relatively common pediatric conditions. This report describes the recommended clinical genetics diagnostic approach. The report is based on a review of published reports, most consisting of medium to large case series of diagnostic tests used, and the proportion of those that led to a diagnosis in such patients.
RCTs		
Montgomery, 2013[38]	422 patients	This study reports a randomized clinical trial evaluating the efficacy of an intervention to prepare individuals to communicate BRCA1/BRCA2 results to family members.
Rothwell, 2012[39]	65 patients	The goal of this pilot feasibility study was designed to test the initial acceptability of group GC on selected patient outcomes (satisfaction, distress, perceived control) in a breast/ovarian cancer genetics clinic setting.
Albada, 2012[40]	101 patients	We conducted a study of the effects of a pre-visit website providing computer-tailored information (E-info gene(ca)), on counselees' expectations, knowledge about breast cancer and heredity and information needs. Counselees were randomized to receive usual care (UC) or UC plus website.
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Fresneau, 2013[28]	20 patients	In 2001, a French expert panel recommended that presymptomatic tests should not be carried out on minors in families affected by Li-Fraumeni syndrome (LFS), flying in the face of possible parental demands for such testing. We decided to investigate the legitimacy of such a recommendation. We aimed to (1) determine the extent to which these doctors were confronted with parental requests for TP53 testing, (2) study how they responded to these requests and the arguments used and (3) assess the attitude of oncogeneticists concerning the normative framework regulating the prescription of tests for minors.
Dhar, 2011[41]	81 patients	To present the outcome of a comprehensive team approach to provide genetic evaluation and testing for a large cohort of children diagnosed with retinoblastoma.

Study	N	Objective
Rasmussen, 2010[17]	109 patients	To explore the benefits and risks of genetic testing in vHL, including among minors.
Case-Control Studies		
None	–	–
Guideline/Conference Proceeding		
Review/Conference Proceeding Coury, 2015[34]	NA	This article summarizes the proceedings of the Autism Speaks conference on Treating the Whole Person with Autism: Care across the Lifespan. The conference was organized with the intent of providing a forum for both families and professionals to learn about the most current research in the field.
Clinical Guideline Schaefer, 2013[35]	NA	The guidelines in this paper have been developed to assist the clinician in the consideration of these factors.
Ongoing Studies (ClinicalTrials.gov)		
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: GC=genetic counseling; N=number of studies/patients; NA=not applicable; NR=not reported; RCTs=randomized controlled trials; vHL=von Hippel-Lindau disease

Appendix Table B-6. Published and ongoing studies potentially relevant to Research Question 6
[How can children in whom a rare disease is suspected (and their caregivers) become better prepared to process relevant health and psychosocial information, understand limitations of this information, decide how to act on this information, and stay informed beyond their initial decision?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Montgomery, 2013[38]	422 patients	This study reports a randomized clinical trial evaluating the efficacy of an intervention to prepare individuals to communicate BRCA1/BRCA2 results to family members.
Albada, 2012[40]	101 patients	We conducted a study of the effects of a pre-visit website providing computer-tailored information (E-info gene(ca)), on counselees' expectations, knowledge about breast cancer and heredity and information needs. Counselees were randomized to receive usual care (UC) or UC plus website.
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Tercyak, 2013[6]	221 patients	Although BRCA1/2 genetic testing is discouraged in minors, mothers may disclose their own results to their children. Factors affecting patients' disclosure decisions and patient outcomes of disclosure are largely unknown.
Bailey, 2013[42]	716 patients	To determine whether a brochure based on principles of informed decision making improved attention to study materials or altered decisions made by parents invited to participate in a fragile X syndrome newborn screening study.
Williams, 2010[14]	433 patients	The aim of this study was to examine benefits reported by people with an HD family history or those who have undergone predictive HD testing, as well as the personal variables associated with perceived benefits.
Duncan, 2010[16]	10 patients	In this paper we present findings from ten in-depth interviews with young people who have undergone predictive genetic testing for FAP (four male, six female; five gene-positive, five gene-negative; aged 10-17 years at the time of their predictive test; aged 12-25 years at the time of their research interview). We present five themes that emerged from the interviews which highlight key ethical challenges associated with such testing.
Rasmussen, 2010[17]	109 patients	To explore the benefits and risks of genetic testing in vHL, including among minors.
Mariotti, 2010[43]	92 patients	In agreement with international guidelines, we tested a protocol for a predictive test to optimize cooperation among specialists, well-being of participants, and organization of clinical activities.
Case-Control Studies		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		

Study	N	Objective
Family Health After Predictive Huntington Disease (HD) Testing (NCT00075140)	422 patients	Completed (October 2008). The purpose of this study is to identify health management concerns and needs of family members of asymptomatic and symptomatic persons with mutation in the gene for Huntington Disease (HD).
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: FAP=familial adenomatous polyposis; HD=Huntington disease; vHL=von Hippel-Lindau disease; N=number of studies/patients; RCTs=randomized controlled trials

Appendix Table B-7. Published and ongoing studies potentially relevant to Research Question 7

[What strategies are most effective in informing shared decision-making with regard to the benefits and risks of pursuing genetic testing in children in whom a rare disease is suspected (and their caregivers)?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Rothwell, 2012[39]	65 patients	The goal of this pilot feasibility study was designed to test the initial acceptability of group GC on selected patient outcomes (satisfaction, distress, perceived control) in a breast/ovarian cancer genetics clinic setting.
Albada, 2012[40]	101 patients	We conducted a study of the effects of a pre-visit website providing computer-tailored information (E-info gene(ca)), on counselees' expectations, knowledge about breast cancer and heredity and information needs. Counselees were randomized to receive usual care (UC) or UC plus website.
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Mand, 2013[5]	9 patients	For the first time, this study reports empirical evidence concerning the process and impacts of predictive testing in mature minors for adult-onset conditions where no medical benefit exists.
Tercyak, 2013[6]	221 patients	Although BRCA1/2 genetic testing is discouraged in minors, mothers may disclose their own results to their children. Factors affecting patients' disclosure decisions and patient outcomes of disclosure are largely unknown.

Study	N	Objective
Fresneau, 2013[28]	20 patients	In 2001, a French expert panel recommended that presymptomatic tests should not be carried out on minors in families affected by Li-Fraumeni syndrome (LFS), flying in the face of possible parental demands for such testing. We decided to investigate the legitimacy of such a recommendation. We aimed to (1) determine the extent to which these doctors were confronted with parental requests for TP53 testing, (2) study how they responded to these requests and the arguments used and (3) assess the attitude of oncogeneticists concerning the normative framework regulating the prescription of tests for minors.
Bailey, 2013[42]	716 patients	To determine whether a brochure based on principles of informed decision making improved attention to study materials or altered decisions made by parents invited to participate in a fragile X syndrome newborn screening study.
Wakefield, 2013[7]	1812 patients	NR
Archibald, 2013[8]	188 patients	This project explored, the views of key stakeholders regarding population-based genetic carrier screening for fragile X syndrome (FXS).
Visootsak, 2012[9]	10 patients	NR
May, 2012[10]	NR	The purpose of this study was to solicit the perspectives of parents who have children with autism about screening for genes associated with aggression, compared to responses from those who have children without disabilities and those planning to have children.
Dhar, 2011[41]	81 patients	To present the outcome of a comprehensive team approach to provide genetic evaluation and testing for a large cohort of children diagnosed with retinoblastoma.
Duncan, 2010[16]	10 patients	In this paper we present findings from ten in-depth interviews with young people who have undergone predictive genetic testing for FAP (four male, six female; five gene-positive, five gene-negative; aged 10-17 years at the time of their predictive test; aged 12-25 years at the time of their research interview). We present five themes that emerged from the interviews which highlight key ethical challenges associated with such testing.
Mariotti, 2010[43]	92 patients	In agreement with international guidelines, we tested a protocol for a predictive test to optimize cooperation among specialists, well-being of participants, and organization of clinical activities.
Case-Control Studies		
None	–	–
Guideline/Conference Proceeding		
Clinical Guideline Schaefer, 2013[35]	NA	The guidelines in this paper have been developed to assist the clinician in the consideration of these factors.

Study	N	Objective
Ongoing Studies (ClinicalTrials.gov)		
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: FAP=familial adenomatous polyposis; GC=genetic counseling; N=number of studies/patients; NA=not applicable; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-8. Published and ongoing studies potentially relevant to Research Question 8

[How does the composition of the care team (e.g., genetic counselors, medical geneticists or other specialist providers, generalist providers, other clinicians) influence outcomes for children receiving genetic testing (and their caregivers)?]

Study	N	Objective
Systematic Reviews		
Moeschler, 2014[37]	NR	Global developmental delay and intellectual disability are relatively common pediatric conditions. This report describes the recommended clinical genetics diagnostic approach. The report is based on a review of published reports, most consisting of medium to large case series of diagnostic tests used, and the proportion of those that led to a diagnosis in such patients.
Waguespack, 2010[23]	NR	To review childhood pheochromocytoma/paraganglioma, including conditions causing genetic predisposition; role of genetic screening discussed.
RCTs		
Rothwell, 2012[39]	65 patients	The goal of this pilot feasibility study was designed to test the initial acceptability of group GC on selected patient outcomes (satisfaction, distress, perceived control) in a breast/ovarian cancer genetics clinic setting.
Cohort Studies		
MacLeod, 2014[1]	61 patients	We looked at the experiences of young people who had had predictive testing for a range of conditions with variable ages at onset and options for screening and treatment.
Krukenberg, 2013[4]	141 patients	Predictive testing for Huntington disease (HD) has been available in the United States (US) since 1987, and the Indiana University Predictive Testing Program has been providing this testing since 1990. To date there has been no published description of those who present for such testing in the US. Here we describe demographics of 141 individuals and reproductive decision making of a subset of 16 of those individuals who underwent predictive HD testing between 1990 and 2010 at one site in the US.

Study	N	Objective
Fresneau, 2013[28]	20 patients	In 2001, a French expert panel recommended that presymptomatic tests should not be carried out on minors in families affected by Li-Fraumeni syndrome (LFS), flying in the face of possible parental demands for such testing. We decided to investigate the legitimacy of such a recommendation. We aimed to (1) determine the extent to which these doctors were confronted with parental requests for TP53 testing, (2) study how they responded to these requests and the arguments used and (3) assess the attitude of oncogeneticists concerning the normative framework regulating the prescription of tests for minors.
Dhar, 2011[41]	81 patients	To present the outcome of a comprehensive team approach to provide genetic evaluation and testing for a large cohort of children diagnosed with retinoblastoma.
Baer, 2010[15]	31,428 patients	To examine the distribution of familial cancer risk and its associations with genetic testing in the United States.
Mariotti, 2010[43]	92 patients	In agreement with international guidelines, we tested a protocol for a predictive test to optimize cooperation among specialists, well-being of participants, and organization of clinical activities.
Case-Control Studies		
None	–	–
Review/Conference Proceeding Coury, 2015[34]	NA	This article summarizes the proceedings of the Autism Speaks conference on Treating the Whole Person with Autism: Care across the Lifespan. The conference was organized with the intent of providing a forum for both families and professionals to learn about the most current research in the field.
Ongoing Studies (ClinicalTrials.gov)		
Standard Genetic Counseling With or Without a Decision Guide in Improving Communication Between Mothers Undergoing BRCA1/2 Testing and Their Minor-Age Children (NCT00685256)	400 patients	Ongoing (estimated completion December 2014). This randomized phase III trial is studying standard genetic counseling given together with a decision guide to see how well it works compared with genetic counseling alone in improving communication between mothers undergoing BRCA1/2 testing and their minor-age children.

Abbreviations not defined above: GC=genetic counseling; N=number of studies/patients; NA=not applicable; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-9. Published and ongoing studies potentially relevant to Research Question 9
[How do shared decision-making processes for genetic testing and patient-centered outcomes differ depending on the types of tests available (e.g., targeted testing for mutations vs. broader approaches like whole-exome or whole-genome sequencing (including the recommendation to analyze and report on the 56 'medically actionable genes')?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
None	–	–
Case-Control Studies		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: N=number of studies/patients; RCTs=randomized controlled trials

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Future Research Prioritization: Implantable Cardioverter Defibrillator Therapy in Older Patients

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ABSTRACT

Over 80% of sudden cardiac deaths (SCDs) occur in patients ≥65 years old; the effectiveness of the implantable cardioverter defibrillator (ICD) in older patients with additional comorbidities beyond older age, as well as the optimal deployment and adoption of ICD in this older population, are uncertain. This report outlines the process for developing a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) as informed by a diverse group of stakeholders on the use of ICDs in older patients (≥70 years of age). Evidence gaps were identified by reviewing existing literature and engaging diverse stakeholders to refine these gaps. Stakeholders ranked evidence gaps by importance from their perspectives using a forced-ranking prioritization method. PubMed was searched for relevant recent studies, and ClinicalTrials.gov was searched for relevant ongoing trials for the highest-ranked evidence gaps. Stakeholders prioritized evidence gaps related to the safety and effectiveness of ICD use in older patient subgroups not well represented in clinical trials, predictors of SCD, impact of ICD use on quality of life, role of shared decision making, disparities in ICD use and referral, risk stratification strategies, patient preferences, and effect of ICD use on geriatric patient-centered outcomes. The degree to which prioritized evidence gaps may have already been addressed is uncertain because a comprehensive systematic review has not been done.

INTRODUCTION

Sudden cardiac death (SCD) is the most common mode of death in the United States; it claims the lives of approximately 350,000 people each year.[1,2] The risk of SCD can be significantly reduced with an implantable cardioverter defibrillator (ICD) as evidenced by several randomized clinical trials.[3-7] Although those trials have informed current practice guidelines on the utilization of primary prevention ICDs, they did not address many areas of immense clinical importance.[8] One of these areas is the efficacy, effectiveness, and safety of the ICD in older patients (≥ 70 years of age). While clinical trials of primary prevention ICDs did not exclude older patients, the mean or median age of patients who were enrolled was well below 70 years of age.[3-7]

In a previous study, our group pooled patient-level data from 5 randomized clinical trials of primary prevention ICDs (n=3,530) and adjusted for known potential confounders.[9] We found that although primary prevention ICDs conferred survival benefit to older patients, this survival advantage attenuated with advancing age. Moreover, the number of patients older than 75 years in that study was relatively small, and this may have affected the results.[9] In an analysis of ICD effectiveness in the American Heart Association Get With the Guidelines- Heart Failure registry database linked with Medicare claims, although receipt of ICD therapy was associated with a lower risk of 3-year mortality in patients 65 to 74 years of age, there was only a trend toward improved survival in patients 75 to 84 years of age (adjusted hazard ratio (HR) 0.65, 95% CI 0.47-0.89 among patients 65 to 74 years; HR 0.80, 95% CI 0.62-1.03 among patients 75-84 years).[10] Therefore, data on the role of primary prevention ICDs in patients ≥ 70 years of age remain inconclusive.

Despite the lack of definitive evidence on the outcomes of primary prevention ICDs in older patients, ICD implantation has become widespread in this population. In the National Cardiovascular Data Registry (NCDR) that captures almost all primary prevention ICD implants in patients 65 years of age and older, the mean age of patients receiving an ICD was 67±13 years.[11] One study of that dataset showed that more than 40% of new ICDs are implanted in patients older than 70 years of age.[12] This underscores the importance of conducting studies aimed at examining the outcomes of primary prevention ICDs in patients ≥ 70 years of age.

There are reasons for why the outcomes of primary prevention ICDs in the elderly may differ from those of their younger counterparts. Older patients who are eligible for a primary prevention ICD because of heart failure typically have other comorbidities that increase the likelihood of non-sudden cardiac death, an outcome not affected by the ICD. Additionally, older patients may be frail and this along with the co-existence of several comorbidities may increase the risk of procedural complications and may have a major negative impact on their quality of life raising concerns about therapies- like the ICD- that prolong life but do not necessarily improve its quality.

Given the clinical importance of SCD, the lack of data regarding the optimal use of ICDs in older patients, the variety of patient-centered outcomes of interest, and areas of uncertainty, we sought to create a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) that would incorporate different stakeholders' perspectives.

A central goal of PCORI is to engage stakeholders in its work in a meaningful way. Between September 2012 and January 2013, PCORI undertook a broad effort to solicit research topics to consider for targeted funding from patients, caregivers, researchers, and results of previous prioritization processes by groups, such as the Institute of Medicine. In 2014, PCORI's Assessment of Prevention, Diagnosis, and Treatment Options program, together with the program's external advisory panel, identified the use of ICDs in older patients as an important topic with unmet research needs. Then, PCORI tasked the Duke University Evidence Synthesis Group (ESG) to work with various stakeholders to identify and prioritize the future research that is most needed by patients and other decision makers on this topic.

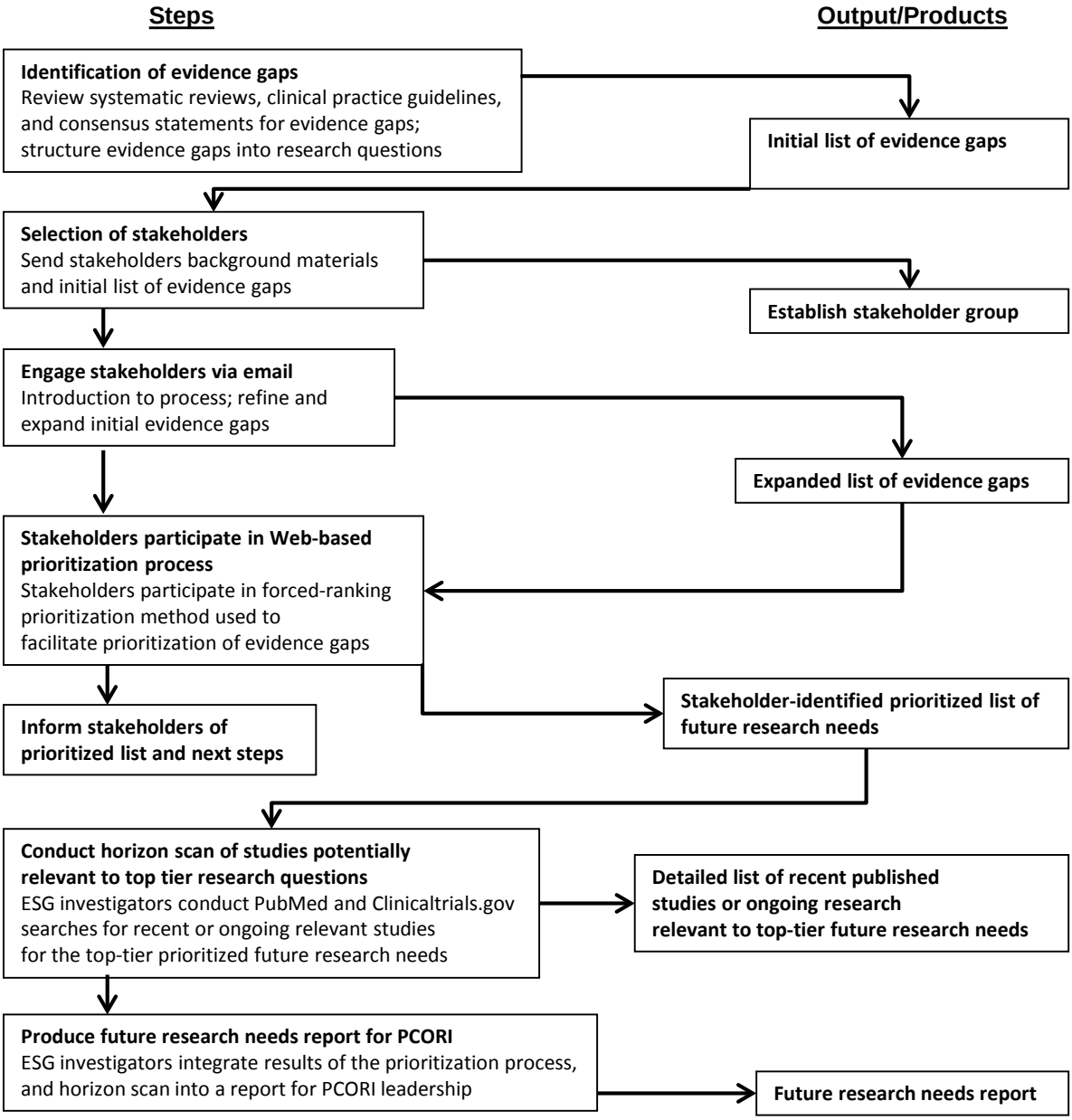
METHODS

Overview of Prioritization Approach

Our approach to prioritizing future research and developing recommendations for targeted future funding by PCORI included several steps (Figure 1). These included appraisals of recent systematic reviews to preliminarily identify important evidence gaps, transformation of evidence gaps into research questions,

engagement of stakeholders to identify additional gaps and prioritize research needs or questions, and scans of recently published and ongoing studies relevant to the stakeholders' list of prioritized research needs.

Figure 1. Overview of prioritization process



Identification of Evidence Gaps

We used an iterative process to identify evidence gaps for ICD use in older patients. First, we identified and appraised recent published systematic reviews, clinical practice guidelines, and future research needs documents to develop an initial list of evidence gaps. This list was neither exhaustive nor prioritized. Next, we organized these gaps according to broad themes and transformed them into research questions.

Selection and Engagement of Stakeholders

We solicited participation from a group of 40 stakeholders, including clinical experts and researchers in the prevention of sudden cardiac death and ICD therapy, representatives from federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision makers and policymakers, and representatives from related consumer and patient advocacy groups (Table 1). Within each of these categories, we sought to identify a person who was either familiar with the clinical area and its current uncertainties or brought a specific methodological expertise to the stakeholder panel. We solicited and received stakeholder input at various points in the process through email detailing the process and outlining existing evidence gaps, and a Web-based survey to obtain priority ranking of topics.

Table 1. Stakeholder organizations and perspectives

Organization	Stakeholder Perspective	Purpose
American College of Cardiology	Professional societies/researchers	The ACC strives to achieve its enduring purpose: to improve cardiovascular health through education, research, quality care and health policy. The members of the College will dramatically reduce the incidence, severity and complications of cardiovascular disease as we promote prevention, reduce disparities in health care, and improve personal and population-based cardiovascular health.
American Heart Association	Professional societies/researchers	The American Heart Association is the nation's oldest, largest voluntary organization devoted to fighting cardiovascular diseases and stroke. Founded by six cardiologists in 1924, the AHA now includes more than 22.5 million volunteers and supporters and funds innovative research, fights for stronger public health policies and provides lifesaving tools and information to save and improve lives.
American Geriatrics Society	Professional societies/researchers	The American Geriatrics Society (AGS) is a not-for-profit organization of over 6,000 health professionals devoted to improving the health, independence and quality of life of all older people. The Society provides leadership to healthcare professionals, policy makers and the public by implementing and advocating for programs in patient care, research, professional and public education, and public policy.
Agency for Healthcare Research and Quality	Healthcare decision- and policy makers	The Agency for Healthcare Research and Quality's (AHRQ) mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used.
Boston Scientific	Product makers	Company which is a leading innovator of medical solutions that improve the health of patients around the world. Products and technologies are used to diagnose or treat a wide range of medical conditions, including heart, digestive, pulmonary, vascular, urological, women's health, and chronic pain conditions.
Heart Rhythm Society	Professional societies/researchers	The Heart Rhythm Society (HRS) is a leading resource on cardiac pacing and electrophysiology. This specialty organization represents medical, allied health, and science professionals from more than 70 countries who specialize in cardiac rhythm disorders.
Medtronic	Product makers	Medtronic is the world's largest medical technology company, offering innovative therapies to fulfill their Mission of alleviating pain, restoring health, and extending life. Their medical therapies, treat cardiac and vascular diseases, diabetes, and neurological and musculoskeletal conditions.

Organization	Stakeholder Perspective	Purpose
National Cardiovascular Data Registry (NCDR)-ICD Registry	Professional societies/researchers	The ICD Registry™ establishes a national standard for understanding treatment patterns, clinical outcomes, device safety, and the overall quality of care provided to implantable cardioverter defibrillator (ICD) patients. As the CMS-mandated registry for hospitals that perform ICD implantation procedures, the ICD Registry plays an important role in determining the association between evidence-based treatment strategies and clinical outcomes. Eighty percent of participating hospitals value the registry beyond the CMS-mandate – capturing all ICD implantations regardless of payer or indication.
National Heart, Lung, Blood Institute	Healthcare decision- and policy makers	The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.
Patient Advocate	Patient advocacy	To represent research priorities and issues from the patient's perspective.
St Jude Medical	Product makers	Company with mission to transform the treatment of expensive epidemic diseases, including atrial fibrillation, heart failure, stroke, coronary artery disease, congenital heart defects, Parkinson's disease and chronic pain. St. Jude Medical provides innovative solutions that reduce the economic burden of costly diseases on health care systems worldwide and provide improved outcomes for patients.
Sudden Cardiac Arrest Association	Consumer and patient advocacy	The Sudden Cardiac Arrest Association (SCAA) is an organization singularly focused on sudden cardiac arrest. SCAA identifies and unites survivors, those at risk of sudden cardiac arrest, as well as others who are interested in being advocates on SCAA issues in their communities and beyond. Our membership is dedicated to promoting solutions to prevent sudden cardiac death, including increased awareness, immediate bystander action, public access to defibrillation (PAD), cardiovascular disease prevention, and access to preventative therapies.
Sudden Cardiac Arrest Thought Alliance	Professional societies/researchers	The Sudden Cardiac Arrest Thought Leadership Alliance (SCATLA) was formed to improve the quality of care around Sudden Cardiac Arrest (SCA) and to share and develop educational tools for patients and healthcare providers.
Women Heart	Consumer and patient advocacy	WomenHeart's mission is to improve the health and quality of life of women living with or at risk of heart disease, and to advocate for their benefit.

Abbreviations not defined above: ACC=American College of Cardiology; AHA=American Heart Association; CMS=Centers for Medicare & Medicaid Services; PAD=Public Access Defibrillation

Prioritization of Future Research

After expansion of the identified research priorities, stakeholders were invited to rank the revised future research needs online. The survey used a forced-ranking prioritization method described by the Agency for Healthcare Research and Quality Evidence-based Practice Center's Future Research Needs projects,[13] whereby participants were given 17 votes that could be allocated to any identified research priorities, with a maximum of 3 votes per item. The stakeholders were not given specific prioritization criteria to use but rather were told to decide, on the basis of their perspectives, which were the most important unanswered research questions in the use of ICD therapy in older patients. We also asked stakeholder to self-report their perspective understanding that an individual stakeholder could represent more than one perspective. Possible perspectives included: patients and the public, providers, purchasers, payers, policymakers, product makers, and principal investigators. Only the priorities in the top tier (n=12) moved on to the final stage of horizon scan. Stakeholders were informed of the final ranking of future research priorities.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

We performed 2 database searches to identify recently published and ongoing studies relevant to the top-tier future research questions resulting from the stakeholder forced-ranking prioritization exercise. We searched PubMed to identify relevant literature published during the past 5 years and ClinicalTrials.gov for ongoing and recently completed studies. For the search of ClinicalTrials.gov, we used the keywords “ICD” OR (“defibrillator” AND “implantable”) and focused on senior populations and Phase 3 or 4 studies. Appendix A provides the exact search strategy used for PubMed.

Members of the ESG team reviewed the titles and abstracts identified by searching PubMed for applicability to the top-tier research questions. Articles were included if they met all of the following criteria: presented original data or secondary analysis of data from an RCT, prospective or retrospective observational study, or relevant modeling study; included data for a related to ICD use and the prevention of sudden cardiac death;

potentially included data on patients aged 65 and older; and had a stated objective that could be categorized according to our identified list of research priorities.

For the ClinicalTrials.gov search, a member of the ESG team reviewed all study abstracts identified by the search and coded them as potentially relevant to 1 or more of the identified research priorities. We then abstracted study type (such as observational or RCT), recruitment status, and sample size.

RESULTS

Expansion of Evidence Gaps Through Stakeholder Engagement

Of the 40 solicited stakeholders, 22 provided input and helped expand the initial list of 22 evidence gaps to 48. The gaps were organized in to 3 broad themes:

1. Evidence gaps in ICD effectiveness in subgroups of older individuals specified by factors besides old age that predispose to increased mortality
2. Evidence gaps in safe deployments of ICDs in older individuals, with and without comorbidities
3. Evidence gaps in adoption of ICDs in older individuals

Stakeholder Ranking of Future Research Needs

Table 2 shows the 48 final potential research topics and stakeholder ranking. Eighteen stakeholders completed the prioritization exercise. We also indicate in Table 2 the number of stakeholders who voted for each specific research topic, and the diverse perspectives represented by these votes. Across the 18 stakeholders, 5 self-identified as patients, 13 as providers, 4 as policy makers, 2 as product makers, and 8 as principal investigators. No stakeholders self-identified as purchasers or payers.

Table 2. Final ranking of future research needs for ICD

Question	Score	Stakeholders, *n*	Perspectives[§]
Top Tier			
1. What is the safety and effectiveness of primary prevention ICDs in older patient subgroups not included or not well represented in clinical trials (e.g., patients with multiple comorbidities, patients with advanced kidney disease, age > 80, etc.)?	20	10	3 patients, 7 providers, 2 policy makers, 2 PIs
2. What are the predictors of SCD vs. those of non-SCD in older primary prevention ICD patients? That is at what level of competing (non-SCD) mortality risk are ICDs no longer effective in reducing all cause-mortality?	15	9	1 patient, 7 providers, 2 policy makers, 5 PIs
3. How do ICD shocks, ICD use and follow-up, and complications of ICD use affect survival and quality of life in older patients? Does the impact vary by age, gender, or co-morbidity status?	15	9	4 patients, 4 providers, 4 policy makers, 3 PIs
4. Does facilitated shared decision making with older patients, their families or caregivers and their providers affect ICD treatment choices and prevention of sudden cardiac death outcomes?*	15	8	4 patients, 4 providers, 2 policy makers, 4 PIs
5. Are there disparities in ICD referrals in older patients by sex, race, or ethnicity?*	13	6	1 patient, 5 providers, 2 policy makers, 1 product maker, 2 PIs
6. What is the comparative safety and effectiveness of risk stratification strategies of older patients for SCD beyond using LVEF?	12	6	1 patient, 6 providers, 2 PIs
7. What are effective methods to reduce healthcare disparities in the use of primary (or secondary) prevention ICDs in older patients?	12	6	1 patient, 5 providers, 3 policy makers, 1 product maker, 1 PI
8. What are patient preferences regarding improved survival from ICDs at the possible cost of comorbidities/complications/suffering vs. shorter survival but with quick and “painless” death?*	12	6	2 patients, 4 providers, 1 policy maker, 3 PIs
9. What is the comparative safety and effectiveness of available devices (transvenous single chamber ICD, transvenous dual chamber ICD, subcutaneous ICD) for an individual older patient based on his/her age, underlying heart disease and the presence of other diseases?	11	7	3 patients, 5 providers, 1 policy maker, 1 product maker, 4 PIs
10. What is the effect of ICD intervention on universal geriatric outcomes such as quality of life, physical activity, independence, fatigue and frailty?*	10	8	2 patients, 6 providers, 1 policy maker, 5 PIs

Question	Score	Stakeholders, *n*	Perspectives[§]
11. Is there an upper age limit for which it becomes futile to expect a benefit from an ICD? That is where the increase in survival is minimal compared to patients without an ICD, and there is no or minimal increase in quality-adjusted life years?*	10	6	5 providers, 1 policy maker, 2 PIs
12. What is the distribution of modes of death in older patients who are eligible for a primary (or secondary) prevention ICD?	9	6	1 patient, 5 providers, 1 policy maker, 4 PIs
Middle Tier			
13. What patient reported outcome metrics for quality of life and device adjustment are most informative in ICD research trials of older patients?*	9	5	1 patient, 3 providers, 3 PIs
14. What is the comparative safety and effectiveness of remote monitoring of ICD devices versus standard clinic visits for older patients seen in clinical practice?	9	4	2 patients, 3 providers, 2 product makers, 2 PIs
15. What is the comparative effectiveness of available methods to enhance communications about ICD deactivation as an ongoing process that starts prior to implant and continues over time as patient's health status and goals of care change?	9	4	1 patient, 3 providers, 1 policy maker, 1 PI
16. Is there a role for subcutaneous ICDs in older patients with a primary or secondary prevention indication for the device?	8	5	1 patient, 4 providers, 1 product maker, 3 PIs
17. What is the comparative effectiveness of various decision support tools to assist patients, caregivers, and providers in determining the appropriate timing for ICD deactivation?*	8	5	2 patients, 3 providers, 1 policy maker, 1 PI
18. How do we optimize the safety of ICDs and leads in older patients?	8	4	1 patient, 2 providers, 2 PIs
19. What factors influence ICD remote monitoring adoption and utilization in older patients?*	8	3	1 patient, 3 providers, 2 product makers, 3 PIs
20. What patient-centered or comorbidity-specific outcomes influence the overall effectiveness of ICDs in older adults?*	7	5	4 providers, 1 policy maker, 3 PIs
21. What is the clinical effectiveness and safety of ICD replacements in older patients who have not had an appropriate shock?*	7	5	1 patient, 4 providers, 1 policy maker, 3 PIs
22. What is the additional value of novel markers (like genetic markers, MRI findings, and biomarkers) to predictive models that utilize clinical and mostly conventional risk factors for the prediction of SCD in older patients?	7	4	4 providers, 2 policy makers, 1 PI

Question	Score	Stakeholders, *n*	Perspectives[§]
23. What is the current utilization of ICDs in eligible patients > 65? What are the barriers to utilization?*	7	4	4 providers, 1 policy maker, 1 product maker, 2 PIs
24. What are patient preferences regarding communications from their health care providers about the benefits and burdens of device therapy and how they might align with their desired outcomes for their health care?	7	4	2 patients, 2 providers, 1 policy maker, 1 PI
25. What evidence is needed to better enable a patient-centric approach to end of life decision making for ICD recipients?*	7	3	2 patients, 2 providers, 1 product maker, 1 PI
26. Are there sex differences in any of the above safety and effectiveness questions regarding ICD therapy in older patients?*	5	3	2 patients, 2 providers, 1 policy maker, 1 PI
27. What is the effect of ICD intervention on cognitive trajectory in persons with mild cognitive impairment/early dementia?*	4	4	1 patient, 2 providers, 1 policy maker, 1 PI
28. What is the comparative safety and effectiveness of strategies to minimize short and long-term complications of ICDs in older patients receiving these devices?	4	3	1 patient, 2 providers, 2 PIs
29. How does remote monitoring of ICDs in older patients impact patient outcomes including quality of life and activity?*	4	2	1 patient, 1 providers, 1 policy maker, 1 product maker, 1 PI
30. Do specific types of patient co-morbidities affect older patients' acceptance of ICD therapy and/or provider willingness to recommend?*	4	2	1 patient, 2 providers, 1 product maker, 2 PIs
31. Is the beneficial effect of the ICD in older patients durable beyond the limited follow-up period of existing clinical trials?	3	3	3 providers, 1 policy maker
32. What is the clinical effectiveness and safety of ICD replacements in older patients who have improved ejection fraction?*	3	2	2 providers, 1 PI
33. What are the most effective, patient centered strategies to reduce anxiety associated with ICD shocks/fear of shocks?*	3	1	1 provider, 1 PI
Lower Tier			
34. Does higher frequency of prior heart failure hospitalizations identify a cohort of older patients who will derive less benefit of ICD therapies?*	2	2	1 provider, 1 policy maker, 1 PI
35. What are the predictors of appropriate ICD shocks in older patients with a secondary prevention ICD?*	2	2	1 patient, 2 providers, 2 PIs

Question	Score	Stakeholders, *n*	Perspectives[§]
36. How do the outcomes of "optimal programming of ICDs" as demonstrated by recent randomized clinical trials in older patients seen in clinical practice compare to those observed in those clinical trials?	2	2	1 patient, 1 policy maker, 1 PI
37. What is the comparative safety and effectiveness of optimally programmed single chamber ICDs as compared to optimally programmed dual chamber ICDs in older patients?	2	2	1 patient, 2 providers, 2 PIs
38. What is the most effective patient-centered management strategy of older ICD patients when devices or leads are recalled?	2	2	2 patients, 1 policy maker
39. What is the most effective, patient centered management strategy for older ICD patients with blood stream or other serious infections?*	2	2	2 providers, 1 PI
40. How can the appropriate utilization of primary prevention ICDs in older patients seen in clinical practice be enhanced?	2	2	2 providers, 1 PI
41. What data from device interrogations are older patients most interested in possessing and why?*	2	1	1 provider, 1 product maker, 1 PI
42. What are the predictors of appropriate ICD shocks in older patients with non-ischemic cardiomyopathy with a primary prevention ICD?*	1	1	1 patient, 1 provider, 1 PI
43. What are the predictors of appropriate ICD shocks in older patients with ischemic heart disease with a primary prevention ICD?*	1	1	1 patient, 1 provider, 1 PI
44. What is the influence of the caretaker on an older patients' health management and outcomes related to the prevention of sudden cardiac death and ICD therapy?*	1	1	1 patient
45. Are there socio-economic factors that differentiate effectiveness of ICD therapy recommendation or patient acceptance in older patients, for example: primary caregiver status, living situation (alone or group setting), family circumstances, etc.?*	1	1	1 provider, 1 PI
46. What changes in patient circumstances would alter older patient's acceptance of ICD therapy?*	1	1	1 provider, 1 PI
47. Does obesity in older patients influence ICD effectiveness or safety?*	0	0	–
48. In older patients with ICDs, what are the clinical benefits and risks of the currently used longer-lasting devices?*	0	0	–

§ "Perspectives" indicates the self-reported perspectives represented by the stakeholders who voted for the individual evidence gaps. Note that an individual stakeholder could self-identify as representing more than one perspective (i.e., he/she could self-identify as both a patient and a provider); for this reason, the number of perspectives does not necessarily equal the number of stakeholders.

* Indicates evidence gaps that were added or substantially revised by stakeholders.

Abbreviations: ICD(s)=implantable cardioverter defibrillator(s); LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; *n*=number (of stakeholders); PI(s)=principal investigator(s); SCD=sudden cardiac death

The top 12 future research needs prioritized by stakeholders were related to the safety and effectiveness of ICDs in older patient subgroups not well-represented in clinical trials, predictors of SCD, the impact of ICD use on quality of life, the use of shared decision making, disparities in ICD referrals, risk stratification strategies, patient preferences, effect of ICD use on geriatric outcomes, and distribution of modes of death in older patients.

Of note, 5 of the top 12 evidence gaps were topics suggested by the stakeholder group, only two topics (both suggested by stakeholders) didn't receive any votes and of the 15 lowest tier topics 11 were suggested by stakeholders perhaps indicating that these topics were of interest to an individual stakeholder but not the broader group. The topics which were prioritized in the highest tier in general had support from all included perspectives.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

The horizon scan demonstrated a high-level match between overall stakeholder priorities and recent or ongoing research. Seven of the top 12 prioritized research needs had more than a dozen recent or ongoing studies. The prioritized areas with the most identified potential studies of interest included the prediction of SCD mortality (n=47), potential risk stratification strategies (n=31), impact of ICD use on survival and quality of life (n=29), and the safety and effectiveness of ICDs in subgroups not well represented in clinical trials (n=27).

Our PubMed search identified 1020 articles. Of these, 121 met our inclusion criteria and included 7 systematic reviews, 2 RCTs, 109 cohort studies, 1 case–control study, and 2 other studies. Sample sizes ranged from 12 to over 250,000. Only 9 studies were active comparator studies, 17 studies either were placebo-controlled or used standard of care as the comparison, and 95 studies had no comparator. Only 3 studies were potentially applicable to the shared decision making topic, and only 2 studies focused on efforts to reduce disparities in ICD referrals. Of note, our horizon scanning did not allow us to determine if the study specifically included data on older patients although studies where the mean age of the included cohort was ≤ 60 years of

age were excluded. Of the 121 included studies, only 23 explicitly focused on older patients or on age as a predictor (shaded grey in Table 2).

Our search of ClinicalTrials.gov yielded 232 studies. Of these, 105 did not appear to meet eligibility based on the ICD use in elderly question (looking at intervention and population fields) and another 40 had been terminated or withdrawn prior to study completion. Of the remaining 87 studies, 16 were open and enrolling and 71 had been completed. We identified 10 protocols as potentially relevant to the top-tier research questions. These protocols were a mix of study designs: 8 RCTs, and 2 nonrandomized, interventional trials. Sample sizes ranged from 85 to 1400 patients.

Two of the prioritized research questions had no identified ongoing studies. These included determining predictors of SCD vs non-SCD in older patients and the topic focusing on exploring modes of death in older patients at risk for SCD. The Tables in Appendix B detail key characteristics of the included PubMed and ClinicalTrials.gov articles separately for each of the top-tier future research needs.

DISCUSSION

This article outlines our process for developing a prioritized research agenda for PCORI as informed by a diverse group of stakeholders. We developed a list of 48 potential future research topics in ICD use in older patients on the basis of the existing literature and with input from various stakeholders. The stakeholders prioritized these topics through a forced-ranking process. We then examined recently published and ongoing studies to identify research relevant to the top 12 future research priorities to assist PCORI in developing future targeted funding opportunities.

Of the top 12 future research priorities, 3 topics (#2, 6 and 12 from Table 2) were directly related to risk stratification. This is not surprising as the decision to recommend a primary prevention ICD to a given patient is currently largely based on a left ventricular ejection fraction of ≤ 35%; the main inclusion criterion in the pivotal randomized clinical trials of primary prevention ICDs.[3-8] However, an appreciable number of patients with an ICD never receive any therapy from it. As such, there is a need for better risk stratification tests in all

patients with systolic heart failure especially the elderly. Because of the presence of several comorbidities in older patients, there are competing modes of death that may reduce the potential benefit from an ICD. Of note, nine previously published studies targeted topic #2 (SCD vs non-SCD) and focused explicitly on older populations, two such studies targeted risk stratification strategies (topic #6), and nine studies in older patients explored modes of death (Appendix B) None of these studies were RCTs but instead were cohort studies normally with no comparator.

Two topics (#5 and 7 from Table 2) of the top 12 future research priorities relate to disparities. This is important as previous papers have shown significant gender and race disparities in the Medicare patient population.[14,15] In a survey of practicing cardiologists in the United States, health care providers were not less likely to recommend an ICD to women and racial minorities, but they were less likely to recommend it to older patients.[16] Although this may reflect the hesitation regarding offering an ICD to patients with several comorbidities and frailty, this has not been confirmed by that or other studies. Therefore, disparities in ICD use in older patients should be examined. Only three published studies targeting older patients focused on exploring disparities, none of the included studies targeted strategies for reducing these disparities.

There is a need to enhance the knowledge of ICD outcomes and factors that could affect them in older patients seen in clinical practice and to improve the process of decision making. The latter need is particularly important as determinants of effective and shared decision making in relation to ICDs are yet to be identified. Our search of the literature shows a dearth of studies (only 3) currently examining this issue. These issues are covered by future research priorities 1, 3, 4, 8, 10 and 11 (Table 2).

Future research priority #10 covers an important topic as although single (involving the insertion of a right ventricular lead only) and dual chamber ICDs (involving the insertion of a right atrial and a right ventricular lead) have been on the market for a long time, it is still uncertain as to whether a dual chamber ICD is superior to a single chamber device. This is important as the type of device could affect important patient outcomes. While several studies have compared the outcomes of a single chamber ICD with those of a dual chamber ICD,

those studies had major limitations, they yielded conflicting results, and they predated the evidence on optimal programming of ICDs.[17-32] Therefore, today's healthcare providers and patients often struggle in making this critical decision of what device type to choose, and professional societies and policy makers are incapable of developing evidence-based recommendations and coverage decisions on this issue.[8,33] These issues are further compounded by the advent of subcutaneous ICDs whose outcomes, especially in the elderly are uncertain. Indeed, the mean age of patients enrolled in studies of subcutaneous ICDs was only 54 years.[34,35] Because older patients are more likely to require pacing that cannot be provided by subcutaneous ICDs, subcutaneous ICDs may not be appropriate for older patients. None of the published studies focusing on different device types targeted elderly patients explicitly.

Our prioritization process is not without limitations. Although we took efforts to be comprehensive, it is possible that the list of future research needs we generated and expanded with stakeholder feedback does not reflect the full range of possible future research. In addition, we engaged a relatively small number of stakeholders. It is also possible that another group of stakeholders might rank the identified future research needs differently. Still, we included a diverse stakeholder panel with a range of expertise in determining these priorities with a particular focus on patient-centered research. Also, because a comprehensive systematic review has not been done for many of the identified evidence gaps, we cannot determine with certainty the degree to which prioritized future research needs have already been addressed.

ICDs are currently the most effective treatment for patients at risk for sudden cardiac death. The optimal and most effective use of these life-saving devices however in the older population is uncertain. A workgroup of 27 stakeholders representing diverse perspectives identified 12 research areas as the highest priority for future research for patient-centered use of ICDs in older patients which, if studied, have the potential to resolve some of the uncertainty surrounding the prevention of sudden cardiac death.

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Appendix A. Pub Med Search Strategy

Search date: December 23, 2014

Set #	Terms	
#1	“Defibrillators, Implantable”[MeSH]	11,586
#2	“Aged”[MeSH] OR “Aged, 80 and over”[MeSH]	2,358,168
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials ”[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) OR (("Decision Support Techniques"[Mesh] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR “evaluation studies”[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal”[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab]) AND ("2000"[Date - Publication] : "3000"[Date - Publication])) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4,821,759
#4	#1 AND #2 AND #3	2594
#5	Limits: English, Date: past 5 years	1020

Appendix B. Supplementary Tables

Note: Table rows shaded in grey represent studies which explicitly target patients ≥ 65 years old.

Appendix Table B-1. Published and ongoing studies potentially relevant to Research Question 1

[What is the safety and effectiveness of primary prevention ICDs in older patient subgroups not included or not well represented in clinical trials (e.g., patients with multiple comorbidities, patients with advanced kidney disease, age > 80, etc.)?]

Study	N	Objective
Systematic Reviews		
Pun, 2014[1]	7 studies	The benefit of a primary prevention implantable cardioverter-defibrillator (ICD) among patients with chronic kidney disease is uncertain.
Makki, 2014[2]	5 studies	To evaluate if ICDs affect total mortality in CKD patients at high risk of sudden cardiac death.
Kong, 2011[3]	4 studies	To evaluate the published data on ICD efficacy at reducing all-cause mortality in patients >/= 65 years and in patients >/= 75 years.
Santangeli, 2010[4]	5 studies	The purpose of this study was to better evaluate the benefit of prophylactic ICD in women by performing a meta-analysis of primary prevention ICD trials that assessed gender differences on the end-points of total mortality, appropriate ICD intervention, and survival benefit of ICD compared with placebo.
RCTs		
Piccini, 2011[5]	712 patients	The purpose of this study was to determine whether the benefit of single-lead conservatively programmed ICD therapy varies as a function of time from MI to ICD implantation.
Cohort		
Al-Khatib, 2014[6]	816 patients	To characterize patients with LVEF between 30% and 35% and compare the survival of those with and without ICDs
Singh, 2014[7]	216 patients	This study assessed the association between prophylactic ICD implantation and survival in individuals with severe CKD.
Suleiman, 2014[8]	2807 patients	To provide real-world data regarding outcomes associated with device-based therapy in a large cohort of elderly patients enrolled in the Israeli ICD Registry.
Jama, 2013[9]	268 patients	To determine whether rates of infection, lead dislodgement, or appropriate or inappropriate implantable cardioverter defibrillator (ICD) shocks are increased in patients with preexisting mild cognitive impairment or dementia
Wasmer, 2013[10]	1621 patients	To evaluate whether there are differences in use and outcome of implantable cardioverter defibrillator (ICD) therapy with or without cardiac resynchronization therapy (CRT) between patients with underlying coronary artery disease (CAD) and non-ischemic dilated cardiomyopathy (DCM).
Yung, 2013[11]	5399 patients	To examine the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.
Chen, 2013[12]	66,974 patients	To assess the impact of baseline heart failure (HF) burden on survival with primary implantable cardioverter-defibrillator (ICD) among Medicare recipients.

Study	N	Objective
Hage, 2013[13]	696 patients	This study examined the association of outcomes with CKD in patients receiving an ICD for primary versus secondary prevention.
Rho, 2012[14]	8337 patients	We evaluated sex differences in mode of death among a large cohort of ambulatory heart failure patients who meet criteria for a primary prevention ICD
Kreuz, 2012[15]	94 patients	To identify new predictors of overall mortality in a Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)-like collective to enhance risk stratification.
Parkash, 2012[16]	717 patients	To determine the utilization rates in a primary prevention implantable cardioverter-defibrillator (ICD)-eligible population and mortality in this group compared with a group that had undergone implantation of this therapy.
Brullmann, 2012[17]	936 patients	The aim of this study was to assess the long-term efficacy of ICD treatment in elderly patients and to identify markers of successful ICD therapy and risk factors of mortality.
Van Rees, 2012[18]	1395 patients	This study assesses implant rates, therapy, adverse events, and survival gain in the elderly primary prevention ICD patient.
Williams, 2011[19]	199 patients	Clinical trials of the implantable cardioverter-defibrillator (ICD) have demonstrated a survival benefit over medical therapy for the prevention of sudden cardiac death, but its benefit in patients with concomitant CKD is unclear.
Mezu, 2011[20]	152 patients	The purpose of this study was to examine the effect of ICDs, age, and multiple co-morbidities on survival in elderly patients who otherwise meet implantation criteria for primary prevention of sudden cardiac death.
Strimel, 2011[21]	380 patients	Patients who underwent initial ICD implantation at age 80 or older between January 1995 and April 2010 for primary SCD prevention were identified.
Khan, 2010[22]	78 patients	We investigated the impact of ICDs on survival in patients with moderate-to-severe CKD, including those requiring dialysis therapy (DT).
Ambardekar, 2010[23]	61 patients	Left ventricular assist device (LVAD) use is becoming increasingly common for patients with end-stage heart failure. However, the rate of implantable cardioverter-defibrillator (ICD) shocks and the effect of these shocks on outcomes in patients with LVADs remain unknown.
Rathod, 2010[24]	1016 patients	Renal disease is associated with increased all-cause mortality and cardiovascular mortality. However, the role of ICD implantation on cardiac mortality in patients with renal disease has not been well studied. Implantable cardioverter-defibrillator (ICD) implantation is protective against cardiac death in a secondary prevention population with renal disease.
Boriani, 2010[25]	4977 patients	We investigated the prevalence of trial-generated profiles for implantable defibrillator or cardiac resynchronization therapy candidacy among HF outpatients; we explored differences between real-world and trial populations and we evaluated 1-year survival without device treatment.

Study	N	Objective
Hernandez, 2010[26]	4685 patients	We identified patients with heart failure who were aged 65 years or older and were eligible for an ICD, had left ventricular ejection fraction of 35% or less, and were discharged alive from hospitals participating in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure and the Get With the Guidelines-Heart Failure quality-improvement programs during the period January 1, 2003, through December 31, 2006. We matched the patients to Medicare claims to examine long-term outcomes.
Case-Control Studies		
None	–	–
Other		
Model Sanders, 2010[27]	NR	We sought to examine the cost-effectiveness of ICD therapy in at-risk patients >or=65 years old.
Ongoing Studies (ClinicalTrials.gov)		
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.
Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (NCT00673842)	1400 patients	Ongoing (estimated completion December 2019). This study will assess whether an implantable defibrillator will increase the likelihood of survival in patients who have had a heart attack in the prior year, have abnormal test results from a 24 hour heart monitor, and who have low normal heart function.
Study of Defibrillation Testing In Patients Undergoing Initial ICD Implantation (NCT01905007)	100 patients	Ongoing (estimated completion December 2014). The primary objective of this study is to compare the composite outcome of total mortality and operative complications in patients who do not undergo defibrillation testing to those who do undergo defibrillation testing at the time of initial ICD implantation.
European Health Economic Trial on Home Monitoring in ICD and CRT-D Patients (EuroEco) (NCT00776087)	416 patients	Ongoing (estimated completion April 2016). BIOTRONIK Home Monitoring (HM) service enables the doctors to safely follow up (FU) their ICD and CRT-D patients in a remote fashion, with fewer in-clinic consultations. This may result in a more efficient FU and cost-savings for the health care payer.
The Use of Dual Chamber ICD With Special Programmed Features to Lower the Risk of Inappropriate Shock (NCT00787800)	100 patients	Completed (December 2011). The RAPTURE Study will determine whether dual chamber defibrillators with atrial prevention and termination therapies, minimized ventricular pacing, and remote monitoring will reduce the rate of inappropriate shocks and improve quality of life compared to optimally programmed back-up pacing only single chamber ICDs when used for primary prevention of sudden cardiac death

Abbreviations not defined above: CKD=chronic kidney disease; CRT-D=cardiac resynchronization therapy-defibrillation; HF=heart failure; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; MI=myocardial infarction; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; SCD=sudden cardiac death

Appendix Table B-2. Published and ongoing studies potentially relevant to Research Question 2
[*What are the predictors of SCD vs. those of non-SCD in older primary prevention ICD patients? That is at what level of competing (non-SCD) mortality risk are ICDs no longer effective in reducing all cause-mortality?]*

Study	N	Objective
Systematic Reviews		
Alba, 2013[28]	72 studies	To identify factors associated with mortality in ICD-HF patients
RCTs		
Piccini, 2011[5]	712 patients	The purpose of this study was to determine whether the benefit of single-lead conservatively programmed ICD therapy varies as a function of time from MI to ICD implantation.
Cohort Studies		
Fumagalli, 2014[29]	6311 patients	To compare the age-related determinants of prognosis in a large population of patients with ICD
Kraaier, 2014[30]	861 patients (development) 706 patients (validation)	To reduce sudden cardiac death, implantable cardioverter-defibrillators (ICDs) are indicated in patients with ischaemic and non-ischaemic dilated cardiomyopathy and a left ventricular ejection fraction (LVEF) implantation) in a consecutive primary prevention population.
Naksuk, 2013[31]	382 patients	To determine whether MADIT II risk score can identify patients with greater mortality in a nontrial "real-world" setting
Bhavnani, 2013[32]	1062 patients	To evaluate the association of the Charlson comorbidity index (CCI) on the prediction of early mortality (EM), death <1 year after ICD implant.
Yung, 2013[11]	5399 patients	To examine the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.
Chen, 2013[12]	66,974 patients	To assess the impact of baseline heart failure (HF) burden on survival with primary implantable cardioverter-defibrillator (ICD) among Medicare recipients.
Chong, 2013[33]	283 patients	To assess if selected clinical markers of organ dysfunction were associated with increased 1-year mortality despite ICD therapy
Habibovic, 2013[34]	1012 patients	To evaluate whether anxiety is predictive of ventricular arrhythmias and all-cause mortality 1 year post ICD implantation.
Brenyo, 2012[35]	1232 patients	QRS fragmentation (fQRS) has been reported as a useful ECG parameter in predicting mortality in high-risk postinfarction patients. Its prognostic value for sudden cardiac death (SCD) and ventricular arrhythmias in ischemic cardiomyopathy (ICM) remains unknown.
Bilchick, 2012[36]	17,991 patients (development) 27,893 patients (validation)	To derive and validate a practical risk model to predict death within 4 years of primary prevention implantable cardioverter-defibrillator (ICD) implantation.
Kreuz, 2012[15]	94 patients	To identify new predictors of overall mortality in a Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)-like collective to enhance risk stratification.

Study	N	Objective
Bender, 2012[37]	317 patients	The aim of this study is to examine if electrocardiographic LVH predicts mortality and incident ventricular arrhythmia in patients with ICM.
Barsheshet, 2012[38]	1191 patients	To explore the 8-year survival benefit of a nonresynchronization implantable cardioverter-defibrillator (ICD) according to a simple risk stratification score.
Van Rees, 2012[39]	900 patients	To construct a risk score out of baseline variables to estimate the risk of death without prior implantable cardioverter defibrillator (ICD) in primary prevention ICD patients with ischaemic heart disease.
Brullmann, 2012[17]	936 patients	The aim of this study was to assess the long-term efficacy of ICD treatment in elderly patients and to identify markers of successful ICD therapy and risk factors of mortality.
Kramer, 2012[40]	2717 patients	To develop and validate a risk prediction score to identify patients at high risk for death within 1 year despite ICD therapy.
Lelakowski, 2012[41]	376 patients	To assess patient survival rate after implantation of an ICD without resynchronisation capability.
Maciag, 2012[42]	121 patients	We analysed the predictive value of clinical factors at the time of implantation for adequate ICD interventions and mortality risk.
Dichtl, 2012[43]	743 patients	Elevated gamma-glutamyltransferase (GGT) is a new risk factor for cardiovascular diseases, but its impact on ventricular tachyarrhythmia occurrence and survival in patients with an implantable cardioverter defibrillator (ICD) is unknown
Williams, 2011[19]	199 patients	Clinical trials of the implantable cardioverter-defibrillator (ICD) have demonstrated a survival benefit over medical therapy for the prevention of sudden cardiac death, but its benefit in patients with concomitant CKD is unclear.
Larsen, 2011[44]	425 patients	To assess the association between ICD shocks and time to death after correction for baseline mortality based on the Seattle Heart Failure Model (SHFM).
Forleo, 2011[45]	394 patients	To evaluate the prognostic value of fQRS in ICD recipients.
Scott, 2011[46]	156 patients	The value of biomarkers in identifying patients' potential for survival benefit from ICD therapy is unknown.
Mezu, 2011[20]	152 patients	The purpose of this study was to examine the effect of ICDs, age, and multiple co-morbidities on survival in elderly patients who otherwise meet implantation criteria for primary prevention of sudden cardiac death.
Van Gelder, 2011[47]	537 patients	We investigated whether primary prevention implantable cardioverter defibrillator (ICD) patients with atrial arrhythmias are at higher risk for ICD shocks and mortality compared to patients without atrial arrhythmias in a subanalysis of the PREPARE study
Tzeis, 2011[48]	236 patients	Depression predicts mortality in patients with coronary artery disease and heart failure. However, its effect on patient outcome in the presence of an implantable cardioverter defibrillator (ICD) has not been investigated.
Haines, 2011[49]	268,701 patients	Develop logistic regression models to identify variables most strongly associated with the risk of acute complications and/or in-hospital death.
Wei, 2011[50]	53,198 patients	We asked whether elevated B-type natriuretic peptide (BNP) level is associated with increased risk of in-hospital mortality

Study	N	Objective
		or cardiac arrest in patients undergoing ICD implantation.
Krahn, 2011[51]	5176 patients	Identifying factors contributing to complications may permit identification of high-risk individuals that warrant incremental monitoring and therapy to attenuate risk.
Lewandowski, 2011[52]	67 patients	T-wave alternans (TWA) analysis is a relatively new method of SCD risk stratification. However, it's prognostic role in patients with ICD has not yet been fully established.
Ng, 2010[53]	424 patients	To identify independent clinical, electrocardiographic, and echocardiographic predictors of death and occurrence of ICD therapy in patients with chronic ischemic cardiomyopathy and ICD for primary prevention.
Kreuz, 2010[54]	94 patients	To identify new predictors of adverse events to enhance risk stratification.
Pedersen, 2010[55]	371 patients	We examined the influence of the distressed personality (Type D) and pre-implantation device concerns on short-term mortality in ICD patients.
Ertel, 2010[56]	225 patients	Two-center retrospective cohort study to assess predictors of one-year mortality in ICD recipients > or = 80 years of age.
Rathod, 2010[24]	1016 patients	Renal disease is associated with increased all-cause mortality and cardiovascular mortality. However, the role of ICD implantation on cardiac mortality in patients with renal disease has not been well studied. Implantable cardioverter-defibrillator (ICD) implantation is protective against cardiac death in a secondary prevention population with renal disease.
Swindle, 2010[57]	26,887 patients	We sought to characterize age-specific practices and outcomes among patients with heart failure undergoing device implantation using a large nationally representative administrative database.
Kao, 2010[58]	507 patients	This study examines the contributions of known predictors of survival and quality of life (QOL) to 1-year survival in ICD recipients
Choy, 2010[59]	1231 patients	We examined the risk of all-cause mortality and sudden cardiac death (SCD) in 1,231 patients after myocardial infarction with left ventricular dysfunction enrolled the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II).
Borleffs, 2010[60]	1036 patients	To assess survival and to construct a baseline mortality risk score in primary prevention implantable cardioverter defibrillator (ICD) patients with non-ischaemic or ischaemic heart disease.
Takahashi, 2010[61]	173 patients	To determine whether the risk for ventricular tachyarrhythmia is gender-dependent in patients with nonischemic dilated cardiomyopathy.
Daniels, 2010[62]	199 patients	To assess baseline electrocardiographic (ECG) findings, arrhythmia episodes, and development of severe nonarrhythmic illness or death in patients aged >or=80 years at ICD implantation, and to compare them with younger patients.
Desai, 2010[63]	529 patients	Incidence of appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure treated with combined cardiac resynchronization plus implantable cardioverter-defibrillator therapy versus implantable cardioverter-defibrillator therapy.

Study	N	Objective
Haugaa, 2010[64]	85 patients	The aim of this study was to investigate whether myocardial strain echocardiography can predict ventricular arrhythmias in patients after myocardial infarction (MI).
Verma, 2010[65]	421 patients	Assess predictors of appropriate implantable cardioverter defibrillator (ICD) therapy in patients receiving primary prevention ICDs.
Boriani, 2010[25]	4977 patients	We investigated the prevalence of trial-generated profiles for implantable defibrillator or cardiac resynchronization therapy candidacy among HF outpatients; we explored differences between real-world and trial populations and we evaluated 1-year survival without device treatment.
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: CKD=chronic kidney disease; ECG=electrocardiogram; HF=heart failure; ICD=implantable cardioverter defibrillator; ICD-HF=implantable cardioverter defibrillator-heart failure; ICM=ischemic cardiomyopathy; LVH=left ventricular hypertrophy; MADIT=multicenter automatic defibrillator implantation trial; MI=myocardial infarction; N=number of studies/patients; RCTs=randomized controlled trials; SCD=sudden cardiac death

Appendix Table B-3. Published and ongoing studies potentially relevant to Research Question 3

[How do ICD shocks, ICD use and follow-up, and complications of ICD use affect survival and quality of life in older patients? Does the impact vary by age, gender, or co-morbidity status?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Piccini, 2011[5]	712 patients	The purpose of this study was to determine whether the benefit of single-lead conservatively programmed ICD therapy varies as a function of time from MI to ICD implantation.
Cohort Studies		
Hoogwegt, 2013[66]	401 patients	Examine the relationship between comorbidity burden and anxiety, depression, and health status in patients with an ICD during the first 12 months post-implantation using a prospective study design.
Deyell, 2013[67]	1698 patients	To examine the association between inappropriate ICD shocks and mortality or heart transplantation in a large population cohort.
Weeke, 2013[68]	1609 patients	To evaluate the incidences of and risk factors predisposing to appropriate and inappropriate shocks and mortality in a 'real-world' population of patients with ischaemic heart disease (IHD) and implantable cardioverter defibrillators (ICD) for primary prevention of sudden cardiac death (SCD)
Wasmer, 2013[10]	1621 patients	To evaluate whether there are differences in use and outcome of implantable cardioverter defibrillator (ICD) therapy with or without cardiac resynchronization therapy (CRT) between patients with underlying coronary artery disease (CAD) and non-ischemic dilated cardiomyopathy (DCM).

Study	N	Objective
Streitner, 2103[69]	561 patients	To compare the outcome after shocks in patients with ischemic cardiomyopathy (ICM) or DCM and defibrillators (ICD) implanted for primary prevention.
Habibovic, 2013[34]	1012 patients	To evaluate whether anxiety is predictive of ventricular arrhythmias and all-cause mortality 1 year post ICD implantation.
Ford, 2012[70]	443 patients	The Florida Shock Anxiety Scale (FSAS) was developed to measure ICD patient shock-related anxiety. Initial psychometric evaluation revealed good reliability and validity. The purpose of this study was to examine the psychometrics of the FSAS in a large US sample of ICD patients.
Carroll, 2012[71]	70 patients	To determine whether preimplant psychosocial, generic health-related quality of life (HRQOL), personality disposition, or demographic factors predicted early postimplant device-specific QOL.
Kleemann, 2012[72]	1411 patients	To evaluate the impact of inappropriate ICD shocks on clinical outcome by comparing ICD shocks triggered by atrial fibrillation (AF) with shocks caused by lead failure.
Yang, 2012[73]	148 patients	We investigated the impact of inappropriate shocks on clinical outcomes.
Habibovic, 2012[74]	395 patients	We examined the prevalence and predictors (clinical variables, personality, and anxiety) of PTSD in ICD patients.
Van Rees, 2012[18]	1395 patients	This study assesses implant rates, therapy, adverse events, and survival gain in the elderly primary prevention ICD patient.
Habibovic, 2011[75]	718 patients	We investigated (i) gender disparities in anxiety and QoL and (ii) the magnitude of the effect of gender vs. New York Heart Association (NYHA) functional class (III/IV), ICD shock, and Type D personality on these outcomes.
Larsen, 2011[44]	425 patients	To assess the association between ICD shocks and time to death after correction for baseline mortality based on the Seattle Heart Failure Model (SHFM).
Tzeis, 2011[48]	236 patients	Depression predicts mortality in patients with coronary artery disease and heart failure. However, its effect on patient outcome in the presence of an implantable cardioverter defibrillator (ICD) has not been investigated.
Dichtl, 2011[76]	1117 patients	The occurrence of ventricular tachyarrhythmia indicating progression of the underlying heart disease, but not the ICD shock itself, has prognostic impact in clinical routine.
Strimel, 2011[21]	380 patients	Patients who underwent initial ICD implantation at age 80 or older between January 1995 and April 2010 for primary SCD prevention were identified.
van Rees, 2011[77]	1544 patients	To assess the incidence, predictors, and outcome of inappropriate shocks in implantable cardioverter-defibrillator (ICD) patients.
Nery, 2010[78]	2417 patients	Evaluate the incidence and risk factors for cardiac device infection (CDI) among consecutive patients implanted with pacemaker (PM) or implantable cardioverter defibrillator (ICD) (including cardiac resynchronization therapy devices)

Study	N	Objective
Ambardekar, 2010[23]	61 patients	Left ventricular assist device (LVAD) use is becoming increasingly common for patients with end-stage heart failure. However, the rate of implantable cardioverter-defibrillator (ICD) shocks and the effect of these shocks on outcomes in patients with LVADs remain unknown.
Bhavnani, 2010[79]	1372 patients	To compare the impact of shock delivery for induced ventricular arrhythmias during implantation defibrillation threshold testing and noninvasive electrophysiology study (NIPS) to clinical shocks on long-term outcomes among patients with ICDs.
Sweeney, 2010[80]	2135 patients	The purpose of this study was to determine whether mortality in ICD patients is influenced by the type of therapy (shocks of ATP) delivered.
Desai, 2010[63]	529 patients	Incidence of appropriate cardioverter-defibrillator shocks and mortality in patients with heart failure treated with combined cardiac resynchronization plus implantable cardioverter-defibrillator therapy versus implantable cardioverter-defibrillator therapy.
Lee, 2010[81]	3340 patients	Although implantable cardioverter-defibrillators are widely used, predictors of procedural complications and the consequences of these events have not been determined.
Kapa, 2010[82]	308 patients	To characterize the effects of ICDs and ICD shocks on psychological outcomes.
Tsai, 2010[83]	1060 patients	To determine complications of ICDs during follow up
Kleemann, 2010[84]	122 patients	To evaluate the prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator (ICD) patients without signs of infection and to analyse the impact of bacterial colonization on the incidence of device infection during follow-up.
Case-Control Studies		
Cengiz, 2010[85]	833 patients	The aim of the present study was to evaluate infection frequency, clinical characteristics, risk factors, and microbiologic and therapeutic features in patients with PM/ICD infections.
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Inappropriate Shock Reduction wIth PARAD+ Rhythm DiScrimination (NCT01410552)	1000 patients	Ongoing (estimated completion September 2017). ISIS- ICD study has been designed to confirm that, with the PARAD+ algorithm, it is possible to have an increase of patients free from inappropriate shocks in a general population implanted for primary or secondary prevention with a dual or tri chamber device during one year follow-up

Study	N	Objective
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.
Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (NCT00673842)	1400 patients	Ongoing (estimated completion December 2019). This study will assess whether an implantable defibrillator will increase the likelihood of survival in patients who have had a heart attack in the prior year, have abnormal test results from a 24 hour heart monitor, and who have low normal heart function.
Study of Defibrillation Testing In Patients Undergoing Initial ICD Implantation (NCT01905007)	100 patients	Ongoing (estimated completion December 2014). The primary objective of this study is to compare the composite outcome of total mortality and operative complications in patients who do not undergo defibrillation testing to those who do undergo defibrillation testing at the time of initial ICD implantation.
European Health Economic Trial on Home Monitoring in ICD and CRT-D Patients (EuroEco) (NCT00776087)	416 patients	Ongoing (estimated completion April 2016). BIOTRONIK Home Monitoring (HM) service enables the doctors to safely follow up (FU) their ICD and CRT-D patients in a remote fashion, with fewer in-clinic consultations. This may result in a more efficient FU and cost-savings for the health care payer.
The Use of Dual Chamber ICD With Special Programmed Features to Lower the Risk of Inappropriate Shock (NCT00787800)	100 patients	Completed (December 2011). The RAPTURE Study will determine whether dual chamber defibrillators with atrial prevention and termination therapies, minimized ventricular pacing, and remote monitoring will reduce the rate of inappropriate shocks and improve quality of life compared to optimally programmed back-up pacing only single chamber ICDs when used for primary prevention of sudden cardiac death
Survival of Patients With Primary Prophylactic ICD Indication (NCT00619593)	504 patients	Completed (July 2014). This trial is designed to (i) improve the knowledge of the group characteristics of patients suffering from 1st appropriate ICD therapy, (ii) but moreover to take additional therapeutic steps to reduce the mortality of this patient population.
Prevention of Inappropriate ICD Shocks (NCT02044315)	201 patients	Completed (December 2012). The aim of the present study is to investigate whether increasing detection zones can effectively reduce inappropriate ICD therapies in primary prevention patients.

Abbreviations not defined above: ATP=antitachycardia pacing; DCM=dilated cardiomyopathy; ICD=implantable cardioverter defibrillator; MI=myocardial infarction; N=number of studies/patients; PM=permanent pacemakers; PTSD=posttraumatic stress disorder; QOL=quality of life; RCTs=randomized controlled trials; SCD=sudden cardiac death

Appendix Table B-4. Published and ongoing studies potentially relevant to Research Question 4

[Does facilitated shared decision making with older patients, their families or caregivers and their providers affect ICD treatment choices and prevention of sudden cardiac death outcomes?]

Study	N	Objective
Systematic Reviews		
None	–	–

Study	N	Objective
RCTs		
Thomas, 2013[86]	59 patients	We hypothesized that a targeted patient-centered educational video could improve knowledge of sudden cardiac arrest (SCA) and ICDs and reduce racial differences in ICD preferences. We conducted a pilot study to assess the feasibility of testing this hypothesis in a randomized trial.
Cohort Studies		
Hickman, 2012[87]	109 patients	Exploratory and confirmatory factor analyses, assessments of the internal reliability consistency, and discriminant validity to establish the decisional regret scale as a reliable and valid measure of decision regret in ICD recipients.
Case-Control Studies		
None	–	–
Other		
Measurement development Hazelton, 2014[88]	104 patients	To create and evaluate a measure of patient-evaluated pros and cons of the ICD, and its relationship to patient decision regarding ICD implantation.
Ongoing Studies (ClinicalTrials.gov)		
Implantable Cardioverter-Defibrillator Use in the VA System (NCT01217827)	100 patients	Completed (December 2013). In this study, via brief clinical reminder placed in the electronic medical record, we ask healthcare providers who have not referred potential candidates for defibrillator the reasons for this decision and provide them with the tools for referral if appropriate.

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; RCTs=randomized controlled trials; VA=Veterans Affairs

Appendix Table B-5. Published and ongoing studies potentially relevant to Research Question 5

[Are there disparities in ICD referrals in older patients by sex, race, or ethnicity?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
Hess, 2013[89]	17,639 patients	To evaluate use of ICD use among patients admitted with HF with LVEF of ICD prior to hospitalization, during hospitalization, or were discharged with plans to undergo ICD placement after hospitalization
Martinell, 2013[90]	390 patients	To describe the use and factors of importance for outcome in relation to ICD use among survivors of ventricular fibrillation (VF).
Havmoeller, 2013[91]	1175 patients	From the on-going Oregon Sudden Unexpected Death Study, we analyzed prospectively identified SCD cases in Multnomah County, Ore
Masoudi, 2012[92]	2621 patients	The extent to which the clinical characteristics and long-term outcomes of unselected, community-based patients with left ventricular systolic dysfunction undergoing primary prevention ICD implantation in a real-world setting compare with those enrolled in the randomized, controlled trials is not well characterized

Study	N	Objective
Parkash, 2012[16]	717 patients	To determine the utilization rates in a primary prevention implantable cardioverter-defibrillator (ICD)-eligible population and mortality in this group compared with a group that had undergone implantation of this therapy.
Al-Khatib, 2012[93]	11,880 patients	The degree to which the overall use of ICD therapy and disparities in use have changed is unclear
Habibovic, 2011[75]	718 patients	We investigated (i) gender disparities in anxiety and QoL and (ii) the magnitude of the effect of gender vs. New York Heart Association (NYHA) functional class (III/IV), ICD shock, and Type D personality on these outcomes.
Tsai, 2011[94]	44,805 patients	To estimate the potentially inappropriate use of implantable cardioverter-defibrillator ICDs in older U.S. adults.
Cook, 2011[95]	1054 patients	To examine whether racial and gender disparities in ICD placement are due to underutilization or overutilization.
LaPointe, 2011[96]	542 patients	The extent and documented reasons for nonuse of ICDs among patients with left ventricular systolic dysfunction are unknown.
Swindle, 2010[57]	26,887 patients	We sought to characterize age-specific practices and outcomes among patients with heart failure undergoing device implantation using a large nationally representative administrative database.
Asghar, 2010[97]	563 patients	Evaluates adherence to guidelines by heart failure clinicians (HFCs) vs general cardiologists (GCs) for use of implantable cardioverter-defibrillators (ICDs), biventricular pacing devices (cardiac resynchronization therapy; CRT), and use of medications for heart failure (HF).
Takahashi, 2010[61]	173 patients	To determine whether the risk for ventricular tachyarrhythmia is gender-dependent in patients with nonischemic dilated cardiomyopathy.
Verma, 2010[65]	421 patients	Assess predictors of appropriate implantable cardioverter defibrillator (ICD) therapy in patients receiving primary prevention ICDs.
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Implantable Cardioverter-Defibrillator Use in the VA System (NCT01217827)	100 patients	Completed (December 2013). In this study, via brief clinical reminder placed in the electronic medical record, we ask healthcare providers who have not referred potential candidates for defibrillator the reasons for this decision and provide them with the tools for referral if appropriate.

Abbreviations not defined above: HF=heart failure; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; N=number of studies/patients; QOL=quality of life; RCTs=randomized controlled trials; SCD=sudden cardiac death; VA=Veterans Affairs

Appendix Table B-6. Published and ongoing studies potentially relevant to Research Question 6

[What is the comparative safety and effectiveness of risk stratification strategies of older patients for sudden cardiac death (SCD) beyond using left ventricular ejection fraction (LVEF)?]

Study	N	Objective
Systematic Reviews		

Study	N	Objective
Katritsis, 2013[98]	NR	To study the effects of very low LVEF and prolonged QRS duration on the mortality benefits of ICD therapy.
RCTs		
None	–	–
Cohort Studies		
Bhavnani, 2014[99]	911 patients	To determine the prognostic significance of pre-implant hyponatremia on the outcomes of death, acute decompensated heart failure (ADHF) and appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular arrhythmias among patients with ICDs.
Kraaier, 2014[30]	861 patients (development) 706 patients (validation)	To reduce sudden cardiac death, implantable cardioverter-defibrillators (ICDs) are indicated in patients with ischaemic and non-ischaemic dilated cardiomyopathy and a left ventricular ejection fraction (LVEF) implantation) in a consecutive primary prevention population.
Naksuk, 2013[31]	382 patients	To determine whether MADIT II risk score can identify patients with greater mortality in a nontrial "real-world" setting
Bhavnani, 2013[32]	1062 patients	To evaluate the association of the Charlson comorbidity index (CCI) on the prediction of early mortality (EM), death <1 year after ICD implant.
Yung, 2013[11]	5399 patients	To examine the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.
Rayatzadeh, 2013[100]	48 patients	To determine whether volumetric LVEF measurement using cardiovascular magnetic resonance imaging (CMR-LVEF) is superior to conventional LVEF measurement using 2-dimensional transthoracic echocardiography (Echo-LVEF) for risk stratifying patients referred for primary prevention ICD.
Brenyo, 2012[35]	1232 patients	QRS fragmentation (fQRS) has been reported as a useful ECG parameter in predicting mortality in high-risk postinfarction patients. Its prognostic value for sudden cardiac death (SCD) and ventricular arrhythmias in ischemic cardiomyopathy (ICM) remains unknown.
Bilchick, 2012[36]	17,991 patients (development) 27,893 patients (validation)	To derive and validate a practical risk model to predict death within 4 years of primary prevention implantable cardioverter-defibrillator (ICD) implantation.
Kreuz, 2012[15]	94 patients	To identify new predictors of overall mortality in a Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)-like collective to enhance risk stratification.
Bender, 2012[37]	317 patients	The aim of this study is to examine if electrocardiographic LVH predicts mortality and incident ventricular arrhythmia in patients with ICM.
Klem, 2012[101]	137 patients	To test whether an assessment of myocardial scarring by cardiac magnetic resonance imaging (MRI) would improve risk stratification in patients evaluated for implantable cardioverter-defibrillator (ICD) implantation.
Barsheshet, 2012[38]	1191 patients	To explore the 8-year survival benefit of a nonresynchronization implantable cardioverter-defibrillator (ICD) according to a simple risk stratification score.

Study	N	Objective
Biasucci, 2012[102]	300 patients	To assess the predictive role of C-reactive protein for SCD or VT/VF in ischaemic patients with the ejection fraction <30% and ICDs.
Van Rees, 2012[39]	900 patients	To construct a risk score out of baseline variables to estimate the risk of death without prior implantable cardioverter defibrillator (ICD) in primary prevention ICD patients with ischaemic heart disease.
Wu, 2012[103]	235 patients	We hypothesized that cardiac magnetic resonance identification of myocardial heterogeneity improves risk stratification through (1) its association with adverse cardiac events independent of clinical factors and biomarker levels and (2) its ability to identify particularly high- and low-risk subgroups.
Theuns, 2012[104]	100 patients	High-sensitivity C-reactive protein (hs-CRP) and B-type natriuretic peptide (BNP) are useful biomarkers for cardiovascular risk stratification.
Kramer, 2012[40]	2717 patients	To develop and validate a risk prediction score to identify patients at high risk for death within 1 year despite ICD therapy.
Lelakowski, 2012[41]	376 patients	To assess patient survival rate after implantation of an ICD without resynchronisation capability.
Maciag, 2012[42]	121 patients	We analysed the predictive value of clinical factors at the time of implantation for adequate ICD interventions and mortality risk.
Dichtl, 2012[43]	743 patients	Elevated gamma-glutamyltransferase (GGT) is a new risk factor for cardiovascular diseases, but its impact on ventricular tachyarrhythmia occurrence and survival in patients with an implantable cardioverter defibrillator (ICD) is unknown
Forleo, 2011[45]	394 patients	To evaluate the prognostic value of fQRS in ICD recipients.
Scott, 2011[46]	156 patients	The value of biomarkers in identifying patients' potential for survival benefit from ICD therapy is unknown.
Van Gelder, 2011[47]	537 patients	We investigated whether primary prevention implantable cardioverter defibrillator (ICD) patients with atrial arrhythmias are at higher risk for ICD shocks and mortality compared to patients without atrial arrhythmias in a subanalysis of the PREPARE study
Haines, 2011[49]	268,701 patients	Develop logistic regression models to identify variables most strongly associated with the risk of acute complications and/or in-hospital death.
Wei, 2011[50]	53,198 patients	We asked whether elevated B-type natriuretic peptide (BNP) level is associated with increased risk of in-hospital mortality or cardiac arrest in patients undergoing ICD implantation.
Lewandowski, 2011[52]	67 patients	T-wave alternans (TWA) analysis is a relatively new method of SCD risk stratification. However, it's prognostic role in patients with ICD has not yet been fully established.
Ng, 2010[53]	424 patients	To identify independent clinical, electrocardiographic, and echocardiographic predictors of death and occurrence of ICD therapy in patients with chronic ischemic cardiomyopathy and ICD for primary prevention.
Kreuz, 2010[54]	94 patients	To identify new predictors of adverse events to enhance risk stratification.

Study	N	Objective
Borleffs, 2010[60]	1036 patients	To assess survival and to construct a baseline mortality risk score in primary prevention implantable cardioverter defibrillator (ICD) patients with non-ischaemic or ischaemic heart disease.
Haugaa, 2010[64]	85 patients	The aim of this study was to investigate whether myocardial strain echocardiography can predict ventricular arrhythmias in patients after myocardial infarction (MI).
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.

Abbreviations not defined above: ECG=electrocardiogram; ICD=implantable cardioverter defibrillator; ICM=ischemic cardiomyopathy; MADIT=multicenter automatic defibrillator implantation trial; LVH=left ventricular hypertrophy; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; VF=ventricular fibrillation; VT=ventricular tachycardia

Appendix Table B-7. Published and ongoing studies potentially relevant to Research Question 7

[What are effective methods to reduce healthcare disparities in the use of primary (or secondary) prevention ICDs in older patients?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
Thomas, 2013[86]	59 patients	We hypothesized that a targeted patient-centered educational video could improve knowledge of sudden cardiac arrest (SCA) and ICDs and reduce racial differences in ICD preferences. We conducted a pilot study to assess the feasibility of testing this hypothesis in a randomized trial.
Cohort Studies		
Ricci, 2013[105]	208 patients	To highlight the social impact and costs for the patients associated with hospital visits for routine device follow-up at the enrollment visit for the TARIFF study
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Implantable Cardioverter-Defibrillator Use in the VA System (NCT01217827)	100 patients	Completed (December 2013). In this study, via brief clinical reminder placed in the electronic medical record, we ask healthcare providers who have not referred potential candidates for defibrillator the reasons for this decision and provide them with the tools for referral if appropriate.

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; RCTs=randomized controlled trials; VA=Veterans Affairs

Appendix Table B-8. Published and ongoing studies potentially relevant to Research Question 8

[What are patient preferences regarding improved survival from ICDs at the possible cost of comorbidities/complications/suffering vs. shorter survival but with quick and "painless" death?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
Fluur, 2013[106]	37 patients	This study explored patients' experiences of complex issues of battery replacement and deactivation of the ICD.
Conelius, 2013[107]	200 patients	To develop and evaluate the psychometric properties of the Attitude Towards Advanced Directive Survey and investigate reliability and validity from its use among ICD patients
Chong, 2013[33]	283 patients	To assess if selected clinical markers of organ dysfunction were associated with increased 1-year mortality despite ICD therapy
Kirkpatrick, 2012[108]	278 patients	To conduct a telephone survey of ICD patients re deactivation of implantable cardioverter defibrillators in terminal illness and end of life care

Study	N	Objective
Morrison, 2010[109]	NR	The objective of this study was to explore hospice and palliative care provider attitudes and experience in managing ICDs and pacemakers for patients near the end of life.
Kramer, 2010[110]	185 patients	The purpose of this study was to identify physicians' experiences and views surrounding the ethical and legal aspects of managing cardiac devices at the end of life.
Kao, 2010[58]	507 patients	This study examines the contributions of known predictors of survival and quality of life (QOL) to 1-year survival in ICD recipients
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Treatment Satisfaction in Implantable Cardioverter Defibrillator Recipients (NCT01230073)	120 patients	Ongoing (estimated completion December 2013). To investigate factors that are associated with patients' willingness to accept the new method of follow-up on a broad basis of ICD recipients and to determine their treatment satisfaction with ICD therapy in a randomised, prospective trial
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-9. Published and ongoing studies potentially relevant to Research Question 9

[What is the comparative safety and effectiveness of available devices (transvenous single chamber ICD, transvenous dual chamber ICD, subcutaneous ICD) for an individual older patient based on his/her age, underlying heart disease and the presence of other diseases?]

Study	N	Objective
Systematic Reviews		
Goncalves, 2013[111]	NR	To evaluate which type of device provides fewer inappropriate shocks (dual chamber versus single chamber) in patients with implantable cardioverter defibrillators (ICDs).
RCTs		
None	–	–
Cohort Studies		

Study	N	Objective
Ruwald, 2013[112]	704 patients	To determine whether implantation of dual-chamber ICD devices decrease the incidence of inappropriate therapy without an unacceptable increase in complications.
Peterson, 2013[113]	32,034 patients	To compare outcomes of single- and dual-chamber ICDs for primary prevention of sudden cardiac death.
Gold, 2012[114]	64 patients	A prospective, multicenter trial comparing simulated sensing performances of the S-ICD system with single- (SC-TV) and dual-chamber transvenous (DC-TV) implantable cardioverter-defibrillator (ICD) systems.
Dewland, 2011[115]	104,049 patients	To compare single- versus dual-chamber implantable cardioverter-defibrillator (ICD) implantation and complication rates in a large, real-world population.
Bardy, 2010[116]	78 patients	To eliminate the need for venous access, we designed and tested an entirely subcutaneous ICD system.
Kleemann, 2010[84]	122 patients	To evaluate the prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator (ICD) patients without signs of infection and to analyse the impact of bacterial colonization on the incidence of device infection during follow-up.
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
The Use of Dual Chamber ICD With Special Programmed Features to Lower the Risk of Inappropriate Shock (NCT00787800)	100 patients	Completed (December 2011). The RAPTURE Study will determine whether dual chamber defibrillators with atrial prevention and termination therapies, minimized ventricular pacing, and remote monitoring will reduce the rate of inappropriate shocks and improve quality of life compared to optimally programmed back-up pacing only single chamber ICDs when used for primary prevention of sudden cardiac death

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-10. Published and ongoing studies potentially relevant to Research Question 10

[What is the effect of ICD intervention on universal geriatric outcomes such as QoL, physical activity, independence, fatigue and frailty?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
Hoogwegt, 2013[66]	401 patients	Examine the relationship between comorbidity burden and anxiety, depression, and health status in patients with an ICD during the first 12 months post-implantation using a prospective study design.
Morken, 2013[117]	12 patients	To describe older ICD recipients' experiences of participating in an exercise training programme.

Study	N	Objective
Habibovic, 2013[34]	1012 patients	To evaluate whether anxiety is predictive of ventricular arrhythmias and all-cause mortality 1 year post ICD implantation.
Ford, 2012[70]	443 patients	The Florida Shock Anxiety Scale (FSAS) was developed to measure ICD patient shock-related anxiety. Initial psychometric evaluation revealed good reliability and validity. The purpose of this study was to examine the psychometrics of the FSAS in a large US sample of ICD patients.
Carroll, 2012[71]	70 patients	To determine whether preimplant psychosocial, generic health-related quality of life (HRQOL), personality disposition, or demographic factors predicted early postimplant device-specific QOL.
Arnous, 2011[118]	71 patients	ICD implantation for primary prevention of sudden cardiac death in patients with left ventricular systolic dysfunction (ejection fraction ICD use in a community heart failure population and to assess the impact on patient's quality of life
Pedersen, 2011[119]	284 patients	To examine 1) the prevalence of chronic anxiety (i.e., patients anxious at implantation and 12 months), and 2) predictors of chronic anxiety.
Suzuki, 2010[120]	90 patients	We evaluated the prevalence and persistence of depression in ICD patients over a 2-year period.
Pedersen, 2010[55]	371 patients	We examined the influence of the distressed personality (Type D) and pre-implantation device concerns on short-term mortality in ICD patients.
Kao, 2010[58]	507 patients	This study examines the contributions of known predictors of survival and quality of life (QOL) to 1-year survival in ICD recipients
Kapa, 2010[82]	308 patients	To characterize the effects of ICDs and ICD shocks on psychological outcomes.
Case-Control Studies		
Cengiz, 2010[85]	833 patients	The aim of the present study was to evaluate infection frequency, clinical characteristics, risk factors, and microbiologic and therapeutic features in patients with PM/ICD infections.
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Treatment Satisfaction in Implantable Cardioverter Defibrillator Recipients (NCT01230073)	120 patients	Ongoing (estimated completion December 2013). To investigate factors that are associated with patients' willingness to accept the new method of follow-up on a broad basis of ICD recipients and to determine their treatment satisfaction with ICD therapy in a randomised, prospective trial

Study	N	Objective
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.
Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (NCT00673842)	1400 patients	Ongoing (estimated completion December 2019). This study will assess whether an implantable defibrillator will increase the likelihood of survival in patients who have had a heart attack in the prior year, have abnormal test results from a 24 hour heart monitor, and who have low normal heart function.
The Use of Dual Chamber ICD With Special Programmed Features to Lower the Risk of Inappropriate Shock (NCT00787800)	100 patients	Completed (December 2011). The RAPTURE Study will determine whether dual chamber defibrillators with atrial prevention and termination therapies, minimized ventricular pacing, and remote monitoring will reduce the rate of inappropriate shocks and improve quality of life compared to optimally programmed back-up pacing only single chamber ICDs when used for primary prevention of sudden cardiac death

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; PM=permanent pacemaker; QOL=quality of life; RCTs=randomized controlled trials

Appendix Table B-11. Published and ongoing studies potentially relevant to Research Question 11

[Is there an upper age limit for which it becomes futile to expect a benefit from an ICD? That is where the increase in survival is minimal compared to patients without an ICD, and there is no or minimal increase in quality-adjusted life years?]

Study	N	Objective
Systematic Reviews		
Kong, 2011[3]	4 studies	To evaluate the published data on ICD efficacy at reducing all-cause mortality in patients >/= 65 years and in patients >/= 75 years.
RCTs		
None	–	–
Cohort Studies		
Fumagalli, 2014[29]	6311 patients	To compare the age-related determinants of prognosis in a large population of patients with ICD
Yung, 2013[11]	5399 patients	To examine the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.
Strimel, 2011[21]	380 patients	Patients who underwent initial ICD implantation at age 80 or older between January 1995 and April 2010 for primary SCD prevention were identified.
Ertel, 2010[56]	225 patients	Two-center retrospective cohort study to assess predictors of one-year mortality in ICD recipients > or = 80 years of age.

Study	N	Objective
Swindle, 2010[57]	26,887 patients	We sought to characterize age-specific practices and outcomes among patients with heart failure undergoing device implantation using a large nationally representative administrative database.
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
Efficacy and Safety of ICD Implantation in the Elderly (NCT02121158)	85 patients	Ongoing (estimated completion February 2016). The overall aim of this trial is to study the safety and efficacy of ICD implantation as a primary prevention strategy of sudden cardiac death in patients 70 years and older. This study will assess the many competing factors involved with ICD implantation including 1) the impact on mortality, especially in the context of a declining rate of sudden death with advanced age, 2) the tolerability of the powerful therapeutic action of the device, and 3) the impact on quality of life.
Efficacy of Implantable Defibrillator Therapy After a Myocardial Infarction (NCT00673842)	1400 patients	Ongoing (estimated completion December 2019). This study will assess whether an implantable defibrillator will increase the likelihood of survival in patients who have had a heart attack in the prior year, have abnormal test results from a 24 hour heart monitor, and who have low normal heart function.

Abbreviations not defined above: ICD=implantable cardioverter defibrillator; N=number of studies/patients; RCTs=randomized controlled trials; SCD=sudden cardiac death

Appendix Table B-12. Published and ongoing studies potentially relevant to Research Question 12

[What is the distribution of modes of death in older patients who are eligible for a primary (or secondary) prevention ICD?]

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
Fumagalli, 2014[29]	6311 patients	To compare the age-related determinants of prognosis in a large population of patients with ICD
Kraaier, 2014[30]	861 patients (development) 706 patients (validation)	To reduce sudden cardiac death, implantable cardioverter-defibrillators (ICDs) are indicated in patients with ischaemic and non-ischaemic dilated cardiomyopathy and a left ventricular ejection fraction (LVEF) implantation) in a consecutive primary prevention population.
Yung, 2013[11]	5399 patients	To examine the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.
Rho, 2012[14]	8337 patients	We evaluated sex differences in mode of death among a large cohort of ambulatory heart failure patients who meet criteria for a primary prevention ICD
Thijssen, 2012[121]	2859 patients	To assess the mode of death in ICD/CRT-D recipients in routine clinical practice.

Study	N	Objective
Brullmann, 2012[17]	936 patients	The aim of this study was to assess the long-term efficacy of ICD treatment in elderly patients and to identify markers of successful ICD therapy and risk factors of mortality.
Larsen, 2011[44]	425 patients	To assess the association between ICD shocks and time to death after correction for baseline mortality based on the Seattle Heart Failure Model (SHFM).
Mezu, 2011[20]	152 patients	The purpose of this study was to examine the effect of ICDs, age, and multiple co-morbidities on survival in elderly patients who otherwise meet implantation criteria for primary prevention of sudden cardiac death.
Strimel, 2011[21]	380 patients	Patients who underwent initial ICD implantation at age 80 or older between January 1995 and April 2010 for primary SCD prevention were identified.
Ertel, 2010[56]	225 patients	Two-center retrospective cohort study to assess predictors of one-year mortality in ICD recipients > or = 80 years of age.
Swindle, 2010[57]	26,887 patients	We sought to characterize age-specific practices and outcomes among patients with heart failure undergoing device implantation using a large nationally representative administrative database.
Daniels, 2010[62]	199 patients	To assess baseline electrocardiographic (ECG) findings, arrhythmia episodes, and development of severe nonarrhythmic illness or death in patients aged >or=80 years at ICD implantation, and to compare them with younger patients.
Hernandez, 2010[26]	4685 patients	We identified patients with heart failure who were aged 65 years or older and were eligible for an ICD, had left ventricular ejection fraction of 35% or less, and were discharged alive from hospitals participating in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure and the Get With the Guidelines-Heart Failure quality-improvement programs during the period January 1, 2003, through December 31, 2006. We matched the patients to Medicare claims to examine long-term outcomes.
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: CRT-D=cardiac resynchronization therapy-defibrillation; ICD=implantable cardioverter defibrillator; N=number of studies/patients; RCTs=randomized controlled trials; SCD=sudden cardiac death

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Future Research Prioritization: Mindfulness-Based Interventions for the Treatment of Anxiety, Depression, and Pain

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ABSTRACT

Chronic pain, depression, and anxiety significantly impact the quality of life of patients. Mindfulness-based interventions refer to exercises, practices, or programs that are typically designed to help individuals learn to focus on attention or awareness and may be effective in helping patients who suffer from chronic pain, depression, and anxiety. This report outlines the process for developing a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) as informed by a diverse group of stakeholders on the use mindfulness-based interventions for the treatment of anxiety, depression, and pain. Evidence gaps were identified by reviewing existing literature and engaging diverse stakeholders to refine these gaps. Stakeholders ranked evidence gaps by importance from their perspectives using a forced-ranking prioritization method. PubMed was searched for relevant recent studies, and ClinicalTrials.gov was searched for relevant ongoing trials for the highest-ranked evidence gaps. Stakeholders prioritized evidence gaps related to the treatment of depression, anxiety, and pain for the following areas: the comparative effectiveness of different mindfulness-based interventions, impact of mindfulness-based interventions on healthcare utilization, adjunctive use of mindfulness-based interventions, positive clinical outcomes associated with mindfulness-based interventions, equivalence testing of mindfulness-based interventions compared to standard of care treatments, comparative safety and effectiveness of mindfulness-based interventions compared to pharmacological and non-pharmacological approaches, differential effectiveness by method of delivery or patient practice, and differential effectiveness by dose and frequency of mindfulness-based interventions. The degree to which prioritized evidence gaps may have already been addressed is uncertain because a comprehensive systematic review has not been done.

INTRODUCTION

Mindfulness-based interventions include exercises, practices, or programs that are designed to help individuals focus on attention or awareness. For example, mindfulness-based stress reduction (MBSR), mindfulness-based cognitive therapy (MBCT), transcendental meditation (TM), other meditation-based interventions; and some forms of prayer tend to focus explicitly on mindfulness training. Other practices such as Tai chi, some forms of yoga, and many types of breathing exercises, on the other hand, may achieve a state of mindfulness indirectly by engaging in a prescribed set of movements or exercises.

Mindfulness-based interventions have been used and studied for a wide range of clinical conditions. The present report focuses on anxiety disorders, depressive disorders, and clinical conditions for which pain is a prominent feature. Anxiety disorders are the most common form of mental disorder, affecting about 40 million American adults each year.[1] Outcomes associated with anxiety disorders include impaired functional status, decreased work productivity, substance abuse, and increased use of health care services.[2] Nearly one-half of those diagnosed with depression are also diagnosed with an anxiety disorder. Depression is the leading cause of disability worldwide, with an estimated global prevalence of 350 million people.[3] Outcomes associated with major depressive disorder include significantly impaired functional status, substance abuse, decreased quality of life, and suicide. Chronic pain affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined—and costs the United States up to $635 billion annually in medical treatment and lost productivity.[4] Outcomes associated with pain include longer hospital stays, increased rates of rehospitalization, increased outpatient visits, and decreased function.

Currently, a combination of medical management and psychotherapy is the mainstay of treatment for depression, anxiety, and pain. Surgical interventions may also be indicated for some pain conditions. Pharmacologic and surgical interventions are often expensive and may be associated with undesirable side effects or adverse events. Psychotherapy is also often expensive and usually requires high levels of commitment and engagement by patients. In contrast, mindfulness interventions are relatively inexpensive and are generally

considered to be relatively safe. Many are also potentially more widely accessible than interventions that must be administered or supervised by a physician, psychologist, or other healthcare professional. The time and resources required to teach a patient specific breathing exercises, or mindfulness meditation techniques, or tai chi movements is not usually excessive.

Given the clinical importance of depression, anxiety, and pain, the lack of data regarding the use of mindfulness as an intervention in these clinical areas, the variety of patient-centered outcomes of interest, and areas of uncertainty, we sought to create a prioritized research agenda for the Patient-Centered Outcomes Research Institute (PCORI) that would incorporate different stakeholders' perspectives.

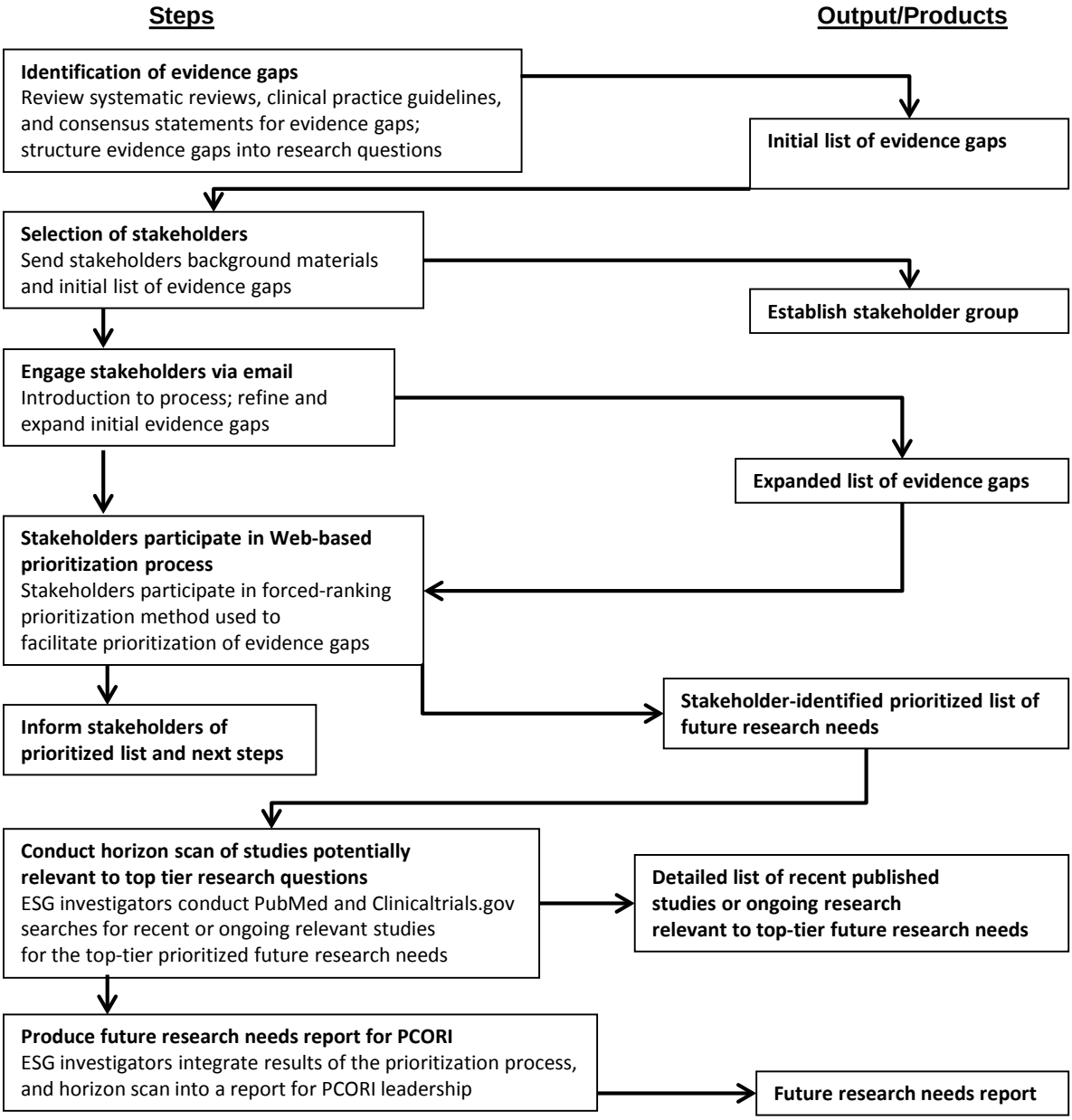
A central goal of PCORI is to engage stakeholders in its work in a meaningful way. Between September 2012 and January 2013, PCORI undertook a broad effort to solicit research topics to consider for targeted funding from patients, caregivers, researchers, and results of previous prioritization processes by groups, such as the Institute of Medicine. In 2014, PCORI's Assessment of Prevention, Diagnosis, and Treatment Options program, together with the program's external advisory panel, identified the use of mindfulness-based interventions for the treatment of anxiety, depression, and pain as an important topic with unmet research needs. Then, PCORI tasked the Duke University Evidence Synthesis Group (ESG) to work with various stakeholders to identify and prioritize the future research that is most needed by patients and other decision makers on this topic.

METHODS

Overview of Prioritization Approach

Our approach to prioritizing future research and developing recommendations for targeted future funding by PCORI included several steps (Figure 1). These included appraisals of recent systematic reviews to preliminarily identify important evidence gaps, transformation of evidence gaps into research questions, engagement of stakeholders to identify additional gaps and prioritize research needs or questions, and scans of recently published and ongoing studies relevant to the stakeholders' list of prioritized research needs.

Figure 1. Overview of prioritization process



Identification of Evidence Gaps

We used an iterative process to identify evidence gaps for mindfulness-based interventions for the treatment of anxiety, depression, and pain. First, we identified and appraised recent published systematic reviews, clinical practice guidelines, and future research needs documents to develop an initial list of evidence gaps. This list was neither exhaustive nor prioritized. Next, we organized these gaps according to broad themes and transformed them into research questions.

Selection and Engagement of Stakeholders

We solicited participation from a group of 20 stakeholders, including clinical experts and researchers in use of mindfulness-based interventions (e.g., mindfulness-based stress reduction [MBSR], mindfulness-based cognitive therapy [MBCT], vipassana, Zen, other mindfulness meditation, qi gong, tai chi, and yoga that includes a mindfulness component), representatives from federal and nongovernmental funding agencies, representatives from relevant professional societies, health care decision makers and policy makers, and representatives from related consumer and patient advocacy groups (Table 1). Within each of these categories, we sought to identify a person who was either familiar with the clinical areas and their current uncertainties or brought a specific methodological expertise to the stakeholder panel. We solicited and received stakeholder input at various points in the process through email detailing the process and outlining existing evidence gaps, and a Web-based survey to obtain priority ranking of topics.

Table 1. Stakeholder organizations and perspectives

Organization	Stakeholder Perspective	Purpose
American Mindfulness Research Association	Professional societies/researchers	Mission is to support empirical and conceptual efforts to establish an evidence base for the process, practice, and construct of mindfulness; promote best evidence-based standards for the use of mindfulness research and its applications; and facilitate mindfulness-related dialogue and discovery. AMRA serves as a professional resource to the sciences and humanities, practice communities, and the broader public on mindfulness from the perspective of contemplative practice.
American Tai Chi Association	Professional societies/researchers	American Tai Chi and Qigong Association (ATCQA), formerly American Tai Chi Association (ATCA), is a national non-profit organization. Its ultimate goal is to promote Tai Chi and Qigong (Chi Kung) - in any style, lineage, or application - in the United States for American people's health, fitness and wellness.
Association for Behavioral and Cognitive Therapies	Professional societies/researchers	The Association for Behavioral and Cognitive Therapies is a multidisciplinary organization committed to the advancement of scientific approaches to the understanding and improvement of human functioning through the investigation and application of behavioral, cognitive, and other evidence-based principles to the assessment, prevention, treatment of human problems, and the enhancement of health and well-being.
Association for Contextual Behavioral Science	Professional societies/researchers	The Association for Contextual Behavioral Science (ACBS) is dedicated to the advancement of functional contextual cognitive and behavioral science and practice so as to alleviate human suffering and advance human well being.
International Association of Yoga Therapists	Professional societies/researchers	The IAYT supports research and education in yoga and yoga therapy and serves as a membership-based, professional organization for yoga teachers and therapists worldwide.
National Center for Complementary and Alternative Medicine	Healthcare decision- and policy makers	The National Center for Complementary and Alternative Medicine (NCCAM) is the Federal Government's lead agency for scientific research on complementary and alternative medicine. The mission of NCCAM is to define, through rigorous scientific investigation, the usefulness and safety of complementary and alternative medicine interventions and their roles in improving health and health care.
National Qigong Association	Professional societies/researchers	The National Qigong (Chi Kung) Association is the premier membership organization for qigong. Serves as an umbrella for all groups, schools, enthusiasts. Western or Eastern. Ancient or Modern.

Organization	Stakeholder Perspective	Purpose
Office of Patient Centered Care, Veterans Health Administration	Healthcare decision- and policy makers	The VA Office of Patient Centered Care and Cultural Transformation (OPCC&CT) works with VA leadership and health care providers to transform VA's health system from the traditional medical model, which focuses on treating specific issues, to a personalized, proactive, patient-driven model that promotes whole health for Veterans and their families.
Patient Advocate	Patient advocacy	To represent research priorities and issues from the patient's perspective.
VA/DoD Integrated Mental Health	Healthcare decision- and policy makers	VA Integrated Mental Health Strategy centers around a coordinated public health model to improve the access, quality, effectiveness, and efficiency of mental health services for all Active Duty Servicemembers, National Guard and Reserve Component members, Veterans, and their families

Abbreviations not defined above: AMRA=American Mindfulness Research Association; DoD=U.S. Department of Defense; IAYT=International Association of Yoga Therapists; VA=U.S. Department of Veterans Affairs

Prioritization of Future Research

After expansion of the identified research priorities, stakeholders were invited to rank the revised future research needs online. The survey used a forced-ranking prioritization method described by the Agency for Healthcare Research and Quality Evidence-based Practice Center's Future Research Needs projects,[5] whereby participants were given 8 votes that could be allocated to any identified research priorities, with a maximum of 3 votes per item. The stakeholders were not given specific prioritization criteria to use but rather were told to decide, on the basis of their perspectives, which were the most important unanswered research questions in the use of mindfulness-based interventions for treatment of anxiety, depression, or pain. We also asked stakeholder to self-report their perspective understanding that an individual stakeholder could represent more than one perspective. Possible perspectives included: patients and the public, providers, purchasers, payers, policy makers, product makers, and principal investigators. Only the priorities in the top tier (n=8) moved on to the final stage of horizon scan. Stakeholders were informed of the final ranking of future research priorities.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

We performed 2 database searches to identify recently published and ongoing studies relevant to the top-tier future research questions resulting from the stakeholder forced-ranking prioritization exercise. We searched

PubMed to identify relevant literature published during the past 5 years and ClinicalTrials.gov for ongoing and recently completed studies. For the search of ClinicalTrials.gov, we used the keywords ("mindfulness" OR "meditation" OR "yoga" OR "mantra" OR "zen" OR "tai chi") AND ("pain" OR "anxiety" OR "depression") and focused on Phase 3 or 4 studies. Appendix A provides the exact search strategy used for PubMed.

Members of the ESG team reviewed the titles and abstracts identified by searching PubMed for applicability to the top-tier research questions. Articles were included if they met all of the following criteria: presented original data or secondary analysis of data from an RCT, prospective or retrospective observational study, selected quasi-experimental studies (pre-/post- designs with or without control groups) or relevant modeling study; included data for a related to a mindfulness intervention for treatment of anxiety, depression, or pain; and had a stated objective that could be categorized according to our identified list of research priorities.

For the ClinicalTrials.gov search, a member of the ESG team reviewed all study abstracts identified by the search and coded them as potentially relevant to 1 or more of the identified research priorities. We then abstracted study type (such as observational or RCT), recruitment status, and sample size.

RESULTS

Expansion of Evidence Gaps Through Stakeholder Engagement

Of the 20 solicited stakeholders, 9 provided input and helped expand the initial list of 14 evidence gaps to 21. The gaps were organized in to 3 broad themes:

4. Mindfulness relative to pharmacological, behavioral, or other currently used therapeutic approaches (including subgroup effects)
5. Mindfulness as adjunctive therapy to existing therapeutic approaches
6. Methods of training or sustaining mindfulness interventions

Evidence gaps added by the stakeholders included question related to differential effects by mode of mindfulness teacher training, treatment sequencing, or characteristics of the programs (e.g., focus on the breath, or focus on sensations, or focus on loving-kindness feelings, meditation, postures/movement, breath regulation),

underling mechanisms through which mindfulness-based interventions exhibit their clinical benefits, measurement issues of mindfulness, and utility of mindfulness-based intervention as compliance and adherence boosters for existing conventional therapies.

Stakeholder Ranking of Future Research Needs

Table 2 shows the 21 final potential research topics and stakeholder ranking. Nine stakeholders completed the prioritization exercise. We also indicate in Table 2 the number of stakeholders who voted for each specific research topic, and the diverse perspectives represented by these votes. Across the 9 stakeholders, 4 self-identified as patients, 6 as providers, 1 as a purchaser, 1 as a policy maker, and 8 and principal investigators. No stakeholders self-identified as product makers or payers.

Table 2. Final ranking of future research needs for mindfulness-based interventions for the treatment of anxiety, depression, and pain

	Question	Score	Stakeholders, *n*	Perspectives[§]
Top Tier				
1.	Which type of mindfulness-based interventions (e.g. meditation, MBSR, MBCT, yoga, tai chi) are most effective for depression, anxiety, or pain?	7	6	3 patients, 4 providers, 1 policy maker, 5 PIs
2.	Do mindfulness-based interventions decrease medication use and other forms of healthcare utilization?	7	5	3 patients, 4 providers, 5 PIs
3.	Are mindfulness-based interventions effective as adjuncts to other commonly used therapies to treat depression, anxiety, or pain (e.g., medical management)? For example, does adjunctive use of mindfulness-based interventions reduce frequency and severity of subsequent disease episodes?	6	6	4 patients, 4 providers, 1 policy maker, 5 PIs
4.	Which mindfulness-based interventions are associated with which favorable clinical outcomes for depression, anxiety or pain? Are these effects maintained (i.e., long-term outcomes) over time?	6	4	2 patients, 3 providers, 1 policy maker, 3 PIs
5.	Do mindfulness-based interventions have equivalent safety and effectiveness compared with standard care for depression, anxiety, or pain?	6	4	2 patients, 2 providers, 4 PIs
6.	What is the comparative safety and effectiveness of mindfulness-based interventions compared to other commonly used strategies (both pharmacologic and non-pharmacological)?	6	4	1 patient, 2 providers, 1 purchaser, 4 PIs
7.	Does the comparative effectiveness of mindfulness-based interventions for depression, anxiety, or pain differ by method of delivery/patient practice (self-help, phone-based, or Internet-based, expert-led group vs. self/home practice)?	5	5	2 patients, 4 providers, 1 purchaser, 1 policy maker, 4 PIs
8.	Does the comparative effectiveness of mindfulness-based strategies for depression, anxiety, or pain differ by dose and frequency of treatment (e.g., length, intensity, frequency, or number of sessions, addition of booster sessions)?	5	3	1 patient, 3 providers, 1 purchaser, 3 PIs
Middle Tier				
9.	What are the most important patient-centered outcomes (e.g., quality of life, pain, productivity, positive outcomes like positive affect, sense of coherence, vitality, sleep quality) for patients with depression, anxiety, or pain that could be impacted by mindfulness-based interventions?	4	4	2 patients, 1 providers, 4 PIs

Question	Score	Stakeholders, *n*	Perspectives[§]
10. Does the addition of mindfulness-based interventions to other commonly used therapies to treat depression, anxiety, or pain (e.g., medical management) decrease medication use and other forms of healthcare utilization?	4	4	1 patient, 2 providers, 1 purchaser, 4 PIs
11. Does adjunctive use of mindfulness-based interventions effectively address secondary clinical symptoms and comorbid conditions (e.g., insomnia, stress, etc.) that are important for patient quality of life and physical and psychological well-being?*	4	4	1 patient, 2 providers, 1 purchaser, 1 policy maker, 3 PIs
12. Does the comparative effectiveness of mindfulness-based interventions for depression, anxiety, or pain differ by methods of training teacher/facilitator?*	3	2	2 patients, 2 providers, 2 PIs
Lower Tier			
13. What are the underling mechanisms through which mindfulness-based interventions exhibit their clinical benefits? Do outcomes differ by underlying mechanisms?*	2	2	1 provider, 1 purchaser, 2 PIs
14. Compared to other interventions, to what extent are the outcomes associated with mindfulness-based interventions attributable to self-reported or objectively measured levels of mindfulness?*	2	2	1 patient, 1 providers, 2 PIs
15. Does the comparative safety and effectiveness of mindfulness-based strategies for depression/anxiety/pain differ by characteristics of the programs (e.g., focus on the breath, or focus on the sensations, or focus on loving-kindness feelings, meditation, postures/movement, breath regulation,)? What is the optimal mix of these components for treating specific conditions?*	2	2	1 provider, 1 policy maker, 1 PI
16. Does the comparative safety and effectiveness of mindfulness-based interventions for depression, anxiety, or pain differ by sequencing of treatments (e.g., pharmacotherapy first then meditation vs. meditation first then pharmacotherapy vs. concurrent)?*	1	1	1 provider, 1 purchaser, 1 PI
17. Do mindfulness-based interventions enhance compliance and adherence to existing conventional therapies (e.g., adherence to prescribed pharmacotherapy or CBT regimen) and thereby improve clinical outcome?*	1	1	1 PI
18. Does the comparative effectiveness of mindfulness-based interventions for depression, anxiety, or pain differ by amount of time spent training patients in the practice?	1	1	1 patient, 1 provider, 1 PI

Question	Score	Stakeholders, *n*	Perspectives[§]
19. Does the comparative safety and effectiveness of mindfulness-based interventions for depression/anxiety/pain differ by patient characteristics or subgroups, such as: a. level of commitment, expectancy, skill, experience with other mindfulness strategies? b. sociodemographic differences (e.g., age/ethnicity, race, socioeconomic status, sex, spiritual disposition or religion)? c. comorbidities? d. underlying disorder/disease (diseases diagnosis, musculoskeletal vs. neuropathic pain) or its severity and/or duration (acute/chronic)?	0	0	–
20. Does the comparative safety and effectiveness of mindfulness-based strategies for depression/anxiety/pain differ when treating one versus treating condition jointly?*	0	0	–
21. What is the comparative effectiveness of patient engagement tools and prompts that promote commitment to mindfulness-based interventions?	0	0	–

[§] "Perspectives" indicates the self-reported perspectives represented by the stakeholders who voted for the individual evidence gaps. Note that an individual stakeholder could self-identify as representing more than one perspective (i.e., he/she could self-identify as both a patient and a provider); for this reason, the number of perspectives does not necessarily equal the number of stakeholders.

* Indicates evidence gaps that were added or substantially revised by stakeholders.

Abbreviations: CBT=cognitive-behavioral therapy; MBCT=mindfulness-based cognitive-behavioral therapy; MBSR=mindfulness-based stress reduction; *n*=number (of stakeholders); PI(s)=principal investigator(s)

The top 8 future research needs prioritized by stakeholders were related to the comparative effectiveness of different mindfulness-based interventions, impact of mindfulness-based interventions on healthcare utilization, adjunctive use of mindfulness-based interventions, positive clinical outcomes associated with mindfulness-based interventions, equivalence testing of mindfulness-based interventions compared to standard of care treatments, comparative safety and effectiveness of mindfulness-based interventions compared to pharmacological and non-pharmacological approaches, differential effectiveness by method of delivery or patient practice, and differential effectiveness by dose and frequency of mindfulness-based interventions.

While all 21 identified evidence gaps received some stakeholder votes, the ones mostly highly ranked by self-identified patients and principal investigators pertained to the comparative effectiveness of different mindfulness-based interventions and the potential benefits of adjunctive use of mindfulness-based interventions (e.g., reduce frequency and severity of subsequent disease episodes, decreased healthcare utilization). None of the seven evidence gaps added by stakeholders was highly prioritized; 2 were ranked in the lower half of the middle tier and 5 were ranked in the lower tier.

Horizon Scan of Studies Potentially Relevant to Top-Tier Research Questions

The horizon scan demonstrated a mismatch between overall stakeholder priorities and recent or ongoing research. Overall, four of the top 8 research needs hade less than a dozen recently published or ongoing trials or observational studies. The research need with the most identified recent or ongoing trials or observational studies (excluding potentially relevant systematic reviews) were positive clinical outcomes associated with mindfulness-based interventions (n=77), comparative safety and effectiveness of mindfulness-based interventions compared to pharmacological and non-pharmacological approaches (n=28), equivalence testing of mindfulness-based interventions compared to standard of care treatments (n=26).

PubMed Search

Our PubMed search identified 841 articles. Of these, 140 met our inclusion criteria and included 38 systematic reviews, 65 RCTs, 11 cohort studies, 1 case–control studies, and 25 of other study designs. Sample

sizes ranged from 5 to 40,428. Only 40 studies were active comparator studies, 58 studies either were placebo-controlled or used standard of care as the comparator, and 20 studies had no comparator. We identified fewer than 10 recently published trials or observational studies for 3 of the top 8 prioritized research areas, the impact of mindfulness-based interventions on healthcare utilization (n=2), differential effectiveness by method of delivery or patient practice (n=4), and differential effectiveness by dose and frequency of mindfulness-based interventions (n=5). Yet, one highly prioritized research need exhibited a relatively large footprint in the recent literature when compared with the other high priority needs; we identified 92 (including 29 systematic reviews or meta-analyses) recently published studies potentially relevant to the topic of positive clinical outcomes associated with mindfulness-based interventions.

ClinicalTrials.gov Search

Our search of ClinicalTrials.gov yielded 36 studies. Of these, 1 did not appear to meet eligibility based on the mindfulness use for anxiety, depression, and pain question (looking at intervention and population fields), and another 2 had been terminated prior to study completion. Of the remaining 33 studies, 13 were open and enrolling and 20 had been completed. We identified 15 protocols as potentially relevant to the top-tier research questions. These protocols were a mix of study designs: 14 randomized interventional trials and 1 nonrandomized interventional trial. Sample sizes ranged from 31 to 460 patients. No high-priority research need had more than 14 identified ongoing or recently completed studies as assessed by a clinicaltrials.gov search. We identified no recently completed or ongoing studies for three of the top 8 prioritized research needs (i.e., impact of mindfulness-based interventions on healthcare utilization, differential effectiveness by method of delivery or patient practice, and differential effectiveness by dose and frequency of mindfulness-based interventions). The prioritized areas with the most identified studies included the positive clinical outcomes associated with mindfulness-based interventions (n=14) and comparative safety and effectiveness of mindfulness-based interventions compared to pharmacological and non-pharmacological approaches (n=8). When rank ordering was taken into account, 3 of the 4 highest-ranked research areas (comparative effectiveness of different

mindfulness-based interventions, impact of mindfulness-based interventions on healthcare utilization, adjunctive use of mindfulness-based interventions,) had 2 or fewer recently completed or ongoing studies.

The Tables in Appendix B detail key characteristics of the included PubMed and ClinicalTrials.gov articles separately for each of the top-tier future research needs.

DISCUSSION

This report outlines our process for developing a prioritized research agenda for PCORI as informed by a diverse group of stakeholders. We developed a list of 21 potential future research topics on mindfulness-based interventions for treatment of anxiety, depression, or pain on the basis of the existing literature and with input from stakeholders. The stakeholders prioritized these topics through a forced-ranking process. We then examined recently published and ongoing studies to identify research relevant to the top 8 future research priorities to assist PCORI in developing future targeted funding opportunities.

Several systematic reviews or evidence maps have been published in recent years that evaluated the effectiveness of a wide variety of mindfulness-based interventions for the treatment of anxiety, depression, and pain. Nearly all of these reviews concluded that there was a need for future studies with rigorous research designs to assess the comparative effectiveness of mindfulness-based interventions to treat anxiety, depression, and pain.[6-8] Our horizon scan findings are consistent with these reviews. Research exploring the effects of mindfulness-based intervention is in its infancy, especially among patients with depressive or anxiety disorders. Overall, we found relatively few ongoing or recently published studies for many of the 8 identified top-tier research needs. Moreover, the majority of recently published studies we identified either had no comparators or used weak control conditions (e.g., usual care) as comparators. Finally, many of the RCTs were comprised of relatively small samples (<100 participants). While the existing literature provides a weak signal of efficacy, it provides limited guidance on the comparative or adjunctive effectiveness of mindfulness-based interventions to inform patient treatment choices.

The overarching theme that emerges from the deliberative process described here is that there is considerable uncertainty about which of the many available mindfulness-based interventions optimize patient-centered outcomes related to depression, anxiety, and pain. Stakeholder input, especially patient input, on research priorities is also consistent with the need for future high-quality comparative effectiveness studies. Three of the 4 highest ranked research questions focus on developing comparative effectiveness research to inform patient treatment choice of mindfulness-based interventions. In contrast, studies focusing on differential effectiveness by dose, frequency, or method of delivery garnered less enthusiastic support from stakeholders.

Mindfulness-based interventions include a wide range of interventions, and anxiety, depression and pain are heterogeneous conditions. Thus, patients are in need of research that can provide guidance on how to select from the varied mindfulness-based interventions that are associated with reducing symptom burden from depression, anxiety, or pain. Both the literature search and our review of ongoing research in ClinicalTrials.gov show a substantial amount of research focused on which mindfulness-based interventions are associated with favorable clinical outcomes for depression, anxiety, or pain, but relatively little research on determining which specific treatment optimizes outcomes.

Our prioritization process is not without limitations. Although we attempted to be comprehensive, it is possible that the list of future research needs we generated and expanded with stakeholder feedback does not reflect the full range of possible future research. In addition, we engaged a relatively small number of stakeholders. It is also possible that another group of stakeholders might rank the identified future research needs differently. Still, we included a diverse stakeholder panel with a range of expertise in determining these priorities with a particular focus on patient-centered research. Also, because a comprehensive systematic review has not been done for many of the identified evidence gaps, we cannot determine with certainty the degree to which prioritized future research needs may already have been addressed.

Mindfulness-based interventions show promise for optimizing patient-centered outcomes related to depression, anxiety, and pain. These interventions are relatively inexpensive and safe. However, the existing

evidence provides little guidance on which mindfulness- based interventions produce the best outcomes for patients. Future research that fills the need for rigorous comparative effectiveness research is required and could help inform which types of mindfulness-based interventions to offer as both first-line treatments and as adjuncts to other evidence-based approaches. Thus, future research should endeavor to directly compare different mindfulness-based interventions and develop high-quality studies that are suited to inform the nature and magnitude of the effectiveness of any one mindfulness-based intervention for one or more of the clinical conditions of interest.

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Appendix A. Pub Med Search Strategy
Search date: December 22, 2014

Set #	Terms	

#1	Mindfulness[MeSH] OR mindfulness[tiab] OR “mindfulness-based”[tiab] OR “Qigong”[MeSH] OR “Tai Ji”[MeSH] OR “Meditation”[MeSH] OR “Yoga”[MeSH] OR “qigong”[tiab] OR “qi gong”[tiab] OR “tai ji”[tiab] OR “tai chi”[tiab] OR “meditation”[tiab] OR “vipassana”[tiab] OR “Zen”[tiab] OR “mantra”[tiab] OR “yoga”[tiab]	8583
#2	(“Anxiety Disorders”[MeSH] OR “Depressive Disorder”[MeSH] OR Pain[MeSH] OR “anxiety”[tiab] OR “depressed”[tiab] OR “depression”[tiab] OR “depressive”[tiab])	719,204
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials “[tiab] OR “comparative study”[Publication Type] OR “comparative study”[tiab] OR systematic[subset] OR “meta-analysis”[Publication Type] OR “meta-analysis as topic”[MeSH Terms] OR “meta-analysis”[tiab] OR “meta-analyses”[tiab]) OR ((“Decision Support Techniques”[Mesh] OR “evaluation studies”[Publication Type] OR “evaluation studies as topic”[MeSH Terms] OR “evaluation study”[tiab] OR “evaluation studies”[tiab] OR “intervention studies”[MeSH Terms] OR “intervention study”[tiab] OR “intervention studies”[tiab] OR “case-control studies”[MeSH Terms] OR “case-control”[tiab] OR “cohort studies”[MeSH Terms] OR cohort[tiab] OR “longitudinal studies”[MeSH Terms] OR “longitudinal”[tiab] OR longitudinally[tiab] OR “prospective”[tiab] OR prospectively[tiab] OR “retrospective studies”[MeSH Terms] OR “retrospective”[tiab] OR “follow up”[tiab]) AND (“2000”[Date - Publication] : “3000”[Date - Publication])) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4,820,663
#4	#1 AND #2 AND #3	1275
#5	Limits: English, Date: past 5 years	829

Appendix B. Supplementary Tables

Appendix Table B-1. Published and ongoing studies potentially relevant to Research Question 1

[Which type of mindfulness-based interventions (e.g., meditation, MBSR, MBCT, yoga, tai chi) are most effective for depression, anxiety, or pain?]

Study	N	Objective
Systematic Reviews		
Sharma, 2014[1]	17 studies	The purpose of this study was to examine studies from 1989 to March 2014 to assess whether tai chi can be an efficacious approach for managing anxiety.
Stratford, 2014[2]	22 studies	This article reviews evidence for the effectiveness of psychological therapy for anxiety in adults with BPSD (bipolar I, II, not otherwise specified, cyclothymia, and rapid cycling disorders).
Wang, 2014[3]	37 studies	A systematic review and meta-analysis were carried out on randomized controlled trials (RCTs) and quasi-experimental (Q-E) trials that studied the effects of tai chi on psychological well-being.
Chugh-Gupta, 2013[4]	25 studies	The aim was to systematically review the evidence concerning the effectiveness of yoga as a treatment approach for state anxiety.
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
Sarris, 2012[6]	NR	The objective of this metareview was to examine evidence across a broad range of CAM and lifestyle interventions in the treatment of anxiety disorders.
Balasubramaniam, 2012[7]	16 studies	To systematically examine the evidence for efficacy of yoga in the treatment of selected major psychiatric disorders.
RCTs		
Crane, 2014[8]	99 patients	Few empirical studies have explored the associations between formal and informal mindfulness home practice and outcome in Mindfulness-based Cognitive Therapy (MBCT). In this study ninety-nine participants randomised to MBCT in a multi-centre randomised controlled trial completed self-reported ratings of home practice over 7 treatment weeks.
la Cour, 2014[9]	109 patients	This randomized controlled clinical trial investigated the effects of mindfulness meditation on chronic pain.
Arch, 2013[10]	105 patients	To compare a mindfulness-based intervention with cognitive behavioral therapy (CBT) for the group treatment of anxiety disorders
Omidi, 2013[11]	90 patients	To evaluate efficacy of Mindfulness Based Cognitive Therapy (MBCT) and traditional Cognitive Behavior Therapy (CBT) with Treatments as usual (TAU) to reduce psychiatric symptoms in a sample of patients with Major Depressive Disorder (MDD)
Cohort Studies		
Serpa, 2014[12]	79 patients	To assess the impact of MBSR on Anxiety, depression, and pain among veterans
Case-Control Studies		
None	–	–
Other		
Uncontrolled pilot (one arm) Goodman, 2014[13]	24 patients	This study examined the feasibility, acceptability, and clinical outcomes of the Coping with Anxiety through Living Mindfully (CALM) Pregnancy intervention.

Study	N	Objective
Non-randomized trial Gangadhar, 2013[14]	137 patients	The study was aimed to compare the therapeutic effect of a generic yoga module with antidepressant drugs in non-suicidal out-patients of major depression attending a psychiatric hospital.
Ongoing Studies (ClinicalTrials.gov)		
Yoga and Qigong for Elderly Patients With Chronic Low Back Pain (NCT01303588)	176 patients	Completed (December 2012). The objective of this study is to evaluate whether yoga or qigong therapy is effective in treating low back pain in elderly patients compared to no therapy (waiting list control). The secondary aim is to compare yoga and qigong.
Comparison of CAM and Conventional Mind-Body Therapies for Chronic Back Pain (NCT01467843)	297 patients	Ongoing (estimated completion September 2015). This trial will evaluate the effectiveness, and cost-effectiveness, of a safe and relatively inexpensive "mind-body" therapy that has the potential to provide relief to some of the millions of Americans who continue to suffer from chronic back pain.

Abbreviations not defined above: BPSD=Bipolar Spectrum Disorder; CAM=Complementary/Alternative Medicine; MABIs=Mindfulness and Acceptance Based Interventions; MBCT=Mindfulness Based Cognitive Therapy; MBSR=Mindfulness Based Stress Reduction; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-2. Published and ongoing studies potentially relevant to Research Question 2

[*Do mindfulness-based interventions decrease medication use and other forms of healthcare utilization?]*

Study	N	Objective
Systematic Reviews		
None	–	–
RCTs		
None	–	–
Cohort Studies		
Kurdyak, 2014[15]	40,428 patients	We compared the impact of Mindfulness Based Cognitive Therapy (MBCT), a structured group treatment, on the rates of health care utilization with matched control participants receiving non-MBCT group therapy.
Ahmed, 2014[16]	19 patients	Performed a retrospective analysis of children undergoing anti-GD2 MoAb 3F8 treatment who received guided meditation
Case-Control Studies		
None	–	–
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: N=number of studies/patients; RCTs=randomized controlled trials

Appendix Table B-3. Published and ongoing studies potentially relevant to Research Question 3
[Are mindfulness-based interventions effective as adjuncts to other commonly used therapies to treat depression, anxiety, or pain (e.g., medical management)? For example, does adjunctive use of mindfulness-based interventions reduce frequency and severity of subsequent disease episodes?]

Study	N	Objective
Systematic Reviews		
Ravindran, 2013[17]	NR	This paper evaluates the risk-benefit profile of CAM augmentation to antidepressants in affective conditions.
Chugh-Gupta, 2013[4]	25 studies	The aim was to systematically review the evidence concerning the effectiveness of yoga as a treatment approach for state anxiety.
Cramer, 2013[18]	10 studies	To systematically review and meta-analyze the effectiveness of yoga for low back pain.
Wang, 2013[19]	12 studies	To evaluate clinical trial evidence of the effectiveness of qigong exercise on depressive and anxiety symptoms
Oh, 2013[20]	10 studies	To evaluate the effects of Qigong on depression.
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
Chen, 2012[21]	36 studies	No review has focused on the efficacy of meditation for anxiety specifically.
Sarris, 2012[6]	NR	The objective of this metareview was to examine evidence across a broad range of CAM and lifestyle interventions in the treatment of anxiety disorders.
Balasubramaniam, 2012[7]	16 studies	To systematically examine the evidence for efficacy of yoga in the treatment of selected major psychiatric disorders.
Bussing, 2012[22]	16 studies	A meta-analysis on the effectiveness of yoga interventions on pain and associated disability.
Posadzki, 2011[23]	7 studies	To assess the effectiveness of yoga as a treatment option for low back pain
RCTs		
Sarubin, 2014[24]	60 patients	The impact of Hatha yoga as add-on treatment to quetiapine fumarate extended release (QXR) or escitalopram (ESC) in depressed patients on hypothalamic-pituitary-adrenal (HPA) axis activity was assessed.
Song, 2014[25]	32 patients	Observe the effect of Tai Chi exercise on the rehabilitation of elder patients suffered from the anxiety disorder.
Kinser, 2013[26]	27 patients	There is a research and clinical imperative to evaluate complementary therapies that are acceptable and feasible for women with depression and that target specific aspects of depression in women, such as ruminations. To begin to address this need, we conducted a randomized, controlled, mixed-methods community-based study comparing an 8-week yoga intervention with an attention-control activity in 27 women with MDD
Michalsen, 2012[27]	77 patients	To evaluate the effectiveness of Iyengar yoga in chronic neck pain by means of a randomized clinical trial.
Yeung, 2012[28]	39 patients	This study examined the feasibility, safety, and efficacy of using tai chi for treating major depressive disorder.
McManus, 2012[29]	74 patients	To assess the impact of mindfulness-based cognitive therapy (MBCT) on health anxiety by comparing the impact of MBCT in addition to usual services (unrestricted services) with unrestricted services (US) alone.

Study	N	Objective
Strauss, 2012[30]	28 patients	Assesses Person-Based Cognitive Therapy (PBCT), an integration of cognitive therapy and mindfulness, as a treatment for chronic depression.
Van Aalderen, 2012[31]	205 patients	To examine the efficacy of mindfulness-based cognitive therapy (MBCT) in addition to treatment as usual (TAU) for recurrent depressive patients with and without a current depressive episode.
Ebnezar, 2012[32]	250 patients	To study the effect of integrated yoga on pain, morning stiffness and anxiety in osteoarthritis of knees.
Sherman, 2011[33]	228 patients	To determine whether yoga is more effective than conventional stretching exercises or a self-care book for primary care patients with chronic low back pain
Lavretsky, 2011[34]	73 patients	In this study, we ask whether a mind-body exercise, Tai Chi Chih (TCC), added to escitalopram will augment the treatment of geriatric depression designed to achieve symptomatic remission and improvements in health functioning and cognitive performance.
Rendant, 2011[35]	123 patients	To evaluate whether qigong is more effective than no treatment and not inferior to exercise therapy.
Cox, 2010[36]	20 patients	To conduct a pilot trial of yoga for the treatment of chronic low back pain (LBP)
Esmer, 2010[37]	25 patients	To evaluate short-term efficacy of MBSR therapy for improving quality of life in adults with failed back surgery syndrome (FBSS)
Vincent, 2010[38]	50 patients	External qigong as a pharmacotherapy adjunct was investigated in 50 subjects with chronic pain
Cohort Studies		
Katzman, 2012[39]	41 patients	To evaluate the efficacy and tolerability of Sudarshan Kriya Yoga (SKY) course in generalized anxiety disorder (GAD) outpatients,
Kim, 2010[40]	23 patients	To examine whether MBCT is effective as an adjunct to pharmacotherapy in the treatment of patients with panic disorder.
Rosenzweig, 2010[41]	133 patients	This study compared changes in bodily pain, health-related quality of life (HRQoL), and psychological symptoms during an 8-week mindfulness-based stress reduction (MBSR) program among groups of participants with different chronic pain conditions.
Case-Control Studies		
None	–	–
Other		
Non-randomized trial Evans, 2013[42]	26 patients	The aim of this study was to assess the impact of a 6-week twice/week Iyengar yoga program on HRQoL of young adults with rheumatoid arthritis compared with a usual-care waitlist control group.
Non-randomized trial Naveen, 2013[43]	NR	To assess the impact of yoga either alone or with antidepressants on depression amoung Non-suicidal, consecutive out-patients of depression
Non-randomized trial Gangadhar, 2013[14]	137 patients	The study was aimed to compare the therapeutic effect of a generic yoga module with antidepressant drugs in non-suicidal out-patients of major depression attending a psychiatric hospital.

Study	N	Objective
Unclear, 2 groups, not RCT Srivastava, 2011[44]	30 patients	To examine the effect of Meditation training on patients with adjustment disorder with anxiety and depression.
Uncontrolled trial Uebelacker, 2010[45]	11 patients	The aim of this study was to assess the acceptability and feasibility of Vinyasa yoga as an adjunctive treatment for depressed patients who were not responding adequately to antidepressant medication.
Non randomized trial Descilo, 2010[46]	183 patients	This study evaluated the effect of a yoga breath program alone and followed by a trauma reduction exposure technique on post-traumatic stress disorder and depression in survivors of the 2004 Asian tsunami.
Ongoing Studies (ClinicalTrials.gov)		
KIDNET vs Meditation/Relaxation - a Dissemination Randomized Controlled Trial for the Treatment of Traumatized Children After War in Sri Lanka (NCT00564317)	48 patients	Completed (January 2006). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children when applied by locally trained teacher counsellors as well as the effectiveness and adequacy of such a treatment in a south-asian war affected stayee child community.
KIDNET Versus Meditation/Relaxation - a Dissemination RCTT for Children in Sri Lanka Traumatized by the War and the Tsunami (NCT00820391)	31 patients	Completed (October 2005). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children in Sri Lanka when applied by locally trained teacher counsellors.

Abbreviations not defined above: CAM=Complementary/Alternative Medicine; HRQoL=Health Related Quality of Life; KIDNET=Kid Narrative Exposure Therapy; MABIs=Mindfulness and Acceptance Based Interventions; MBCT=Mindfulness Based Cognitive Therapy; MBSR=Mindfulness Based Stress Reduction; MDD=Major Depressive Disorder; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; RCTT=Randomized Controlled Treatment Trial

Appendix Table B-4. Published and ongoing studies potentially relevant to Research Question 4

[Which mindfulness interventions are associated with which favorable clinical outcomes for depression, anxiety or pain? Are these effects maintained (i.e., long-term outcomes) over time?]

Study	N	Objective
Systematic Reviews		
Galante, 2014[47]	22 studies	Our aim was to systematically review and meta-analyze the evidence available from randomized controlled trials (RCTs) comparing the effects of Kindness-based meditation on health and well-being against passive and active control groups in patients and the general population.
Stratford, 2014[2]	22 studies	This article reviews evidence for the effectiveness of psychological therapy for anxiety in adults with BPSD (bipolar I, II, not otherwise specified, cyclothymia, and rapid cycling disorders).
Hempel, 2014[48]	107 studies	This evidence map provides an overview of Tai Chi research and describes its volume and focus. It combines a systematic review of systematic reviews with a scoping review for the VA priority areas pain, posttraumatic stress disorder, and fall prevention

Study	N	Objective
Wang, 2014[3]	37 studies	A systematic review and meta-analysis were carried out on randomized controlled trials (RCTs) and quasi-experimental (Q-E) trials that studied the effects of tai chi on psychological well-being.
Orme-Johnson, 2014[49]	16 studies	This meta-analysis of randomized controlled trials (RCTs) on the Transcendental Meditation(R) (TM) technique updates previous meta-analyses and assesses the effects of initial anxiety level, age, duration of practice, regularity of practice, research quality, author affiliation, and type of control group on effect sizes.
Norton, 2014[50]	9 studies	To conduct a Systematic review of studies investigating an mindfulness and acceptance-based treatments for the treatment of social anxiety disorder (SAD)
Abbott, 2014[51]	9 studies	To determine the effectiveness of mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT) on psychological and physical outcomes for people with vascular disease.
Cavanagh, 2014[52]	15 studies	This paper presents a systematic review and meta-analysis of studies that have evaluated the effectiveness and acceptability of low-intensity (self-help) interventions including mindfulness and acceptance-based components.
Goyal, 2014[53]	47 studies	To determine the efficacy of meditation programs in improving stress-related outcomes (anxiety, depression, stress/distress, positive mood, mental health-related quality of life, attention, substance use, eating habits, sleep, pain, and weight) in diverse adult clinical populations
Strauss, 2014[54]	12 studies	This paper presents a meta-analysis of randomised controlled trials (RCTs) of MBIs where participants met diagnostic criteria for a current episode of an anxiety or depressive disorder.
Goyal, 2014[55]	41 studies	We aimed to determine the efficacy and safety of meditation programs on stress-related outcomes (e.g., anxiety, depression, stress, distress, well-being, positive mood, quality of life, attention, health-related behaviors affected by stress, pain, and weight) compared with an active control in diverse adult clinical populations
Querstret, 2013[56]	19 studies	This systematic review aimed to assess treatments used to reduce worry and/or rumination.
Lauche, 2013[57]	6 studies	This paper presents a systematic review and meta-analysis of the effectiveness of mindfulness-based stress reduction (MBSR) for fibromyalgia syndrome
Ward, 2013[58]	17 studies	The current review investigates the effectiveness of yoga on primary outcomes of functional ability, pain and psychosocial outcomes across a range of Musculoskeletal conditions
Cramer, 2013[59]	12 studies	The aim of this review was to systematically assess and meta-analyze the effectiveness of yoga for depression.
Holtzman, 2013[60]	8 studies	To evaluate the efficacy of yoga as an intervention for chronic low back pain (CLBP) using a meta-analytical approach.
Hill, 2013[61]	4 studies	To assess randomized-control trials (RCTs) to ascertain whether yoga is an effective treatment in the management of patients with chronic low back pain (cLBP) compared with other care modalities.

Study	N	Objective
Cramer, 2013[18]	10 studies	To systematically review and meta-analyze the effectiveness of yoga for low back pain.
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
Sarris, 2012[6]	NR	The objective of this metareview was to examine evidence across a broad range of CAM and lifestyle interventions in the treatment of anxiety disorders.
Balasubramaniam, 2012[7]	16 studies	To systematically examine the evidence for efficacy of yoga in the treatment of selected major psychiatric disorders.
Cramer, 2012[62]	3 studies	To conduct a systematic review of the effectiveness of MBSR in low back pain.
Fjorback, 2011[63]	21 studies	To systematically review the evidence for MBSR and MBCT.
Piet, 2011[64]	6 studies	By means of a meta-analysis to evaluate the effect of MBCT for prevention of relapse or recurrence among patients with recurrent MDD in remission.
Chiesa, 2011[65]	NR	The aim of the present work is to review and conduct a meta-analysis of the current findings about the efficacy of MBCT for psychiatric patients.
Chiesa, 2011[66]	10 studies	The aim of the present article is to review controlled studies investigating the efficacy of MBIs for the reduction of pain and the improvement of depressive symptoms in patients suffering from chronic pain.
Cabral, 2011[67]	10 studies	To examine the efficacy of yoga therapy as a complementary treatment for psychiatric disorders such as schizophrenia, depression, anxiety, and posttraumatic stress disorder (PTSD).
Uebelacker, 2010[68]	8 studies	The purpose of this article is to review the evidence for the efficacy of hatha yoga for depression and possible mechanisms by which yoga may have an impact on depression, and to outline directions for future research.
Hofmann, 2010[69]	39 studies	Our objective was to conduct an effect size analysis of mindfulness based therapy for anxiety and mood symptoms in clinical samples.
RCTs		
Thompson, 2014[70]	128 patients	This study evaluated the efficacy of a mindfulness-based cognitive therapy intervention for preventing major depressive disorder (MDD) episodes in people with epilepsy.
Crane, 2014[8]	99 patients	Few empirical studies have explored the associations between formal and informal mindfulness home practice and outcome in Mindfulness-based Cognitive Therapy (MBCT). In this study ninety-nine participants randomised to MBCT in a multi-centre randomised controlled trial completed self-reported ratings of home practice over 7 treatment weeks.
Forkmann, 2014[71]	130 patients	Aim of the present study was to investigate the effects of mindfulness-based cognitive therapy (MBCT) on suicidal ideation in an open-label randomised controlled trial of patients with residual depressive symptoms.
Fleer, 2014[72]	46 patients	The aim of the study is to gain preliminary insight in the efficacy of Mindfulness Based Cognitive Therapy (MBCT) in the prevention of SAD recurrence.

Study	N	Objective
Hosseinzadeh, 2014[73]	NR	The present study aimed at examining the effect of Mindfulness-Based Cognitive Therapy (MBCT) in decreasing depression symptoms in dully diagnosed males (drug dependent males with co-morbid depression).
Wells, 2014[74]	19 patients	Our objective was to assess the safety, feasibility, and effects of the standardized 8-week mindfulness-based stress reduction (MBSR) course in adults with migraines.
Tovote, 2014[75]	94 patients	The aim of this study was to assess the efficacy of individual mindfulness-based cognitive therapy (MBCT) and individual cognitive behavior therapy (CBT) in comparison with a waiting-list control condition for treating depressive symptoms in adults with type 1 or type 2 diabetes.
Newham, 2014[76]	59 patients	This study tested the efficacy of yoga as an intervention for reducing maternal anxiety during pregnancy.
Bedard, 2014[77]	NR	We sought to determine if we could reduce symptoms of depression in individuals with a traumatic brain injury using mindfulness-based cognitive therapy.
Van Son, 2014[78]	139 patients	The DiaMind trial showed beneficial immediate effects of mindfulness-based cognitive therapy (MBCT) on emotional distress, but not on diabetes distress and HbA1c. The aim of the present report was to examine if the effects would be sustained after six month follow-up.
Meadows, 2014[79]	203 patients	The aim of this study was to investigate within a pragmatic study design the effectiveness of MBCT on depressive relapse/recurrence over 2 years of follow-up.
Boettcher, 2014[80]	99 patients	The current trial aims at evaluating the efficacy of a stand-alone, unguided, Internet-based mindfulness treatment program for anxiety.
Ussher, 2014[81]	55 patients	MBSR typically entails an intensive 8-week intervention. The effects of very brief mindfulness interventions are unknown. Among those with chronic pain, the immediate effects of a 10 min mindfulness-based body scan were compared with a control intervention.
Ly, 2014[82]	81 patients	To evaluate and compare the effectiveness of two smartphone-delivered treatments: one based on behavioural activation (BA) and other on mindfulness.
Donald, 2014[83]	45 patients	The present study aimed to investigate the efficacy of Attention Training in comparison to an established treatment for social phobia, Cognitive Therapy.
Pots, 2014[84]	151 patients	The present study evaluates a community-based MBCT intervention for adults with mild to moderate depressive symptomatology in a large multi-site, pragmatic randomized controlled trial.
Guardino, 2014[85]	47 patients	This randomised controlled pilot trial tested a six-week mindfulness-based intervention in a sample of pregnant women experiencing high levels of perceived stress and pregnancy anxiety.
Parthasarathy, 2014[86]	45 patients	Forty-five women with anxiety selected by a random sampling method were divided into three groups. Experimental group I was subjected to asanas, relaxation and pranayama while Experimental group II was subjected to an integrated yoga module.

Study	N	Objective
Morgan, 2014[87]	NR	The current study examined the relationships between separate single item measurements of three types of mindfulness practices (formal, informal, and mindfulness of breath in daily life) and longer-term outcomes in worry, clinician-rated anxiety severity, and quality of life following treatment with an acceptance-based behavior therapy (ABBT) for Generalized Anxiety Disorder (GAD) in two separate treatment studies.
Martins, 2014[88]	60 patients	The objective of this study was to assess the effectiveness of Hatha yoga in the reduction of lumbopelvic pain in pregnancy.
Kocovski, 2013[89]	137 patients	The purpose of the present study was to compare mindfulness and acceptance-based group therapy (MAGT) with cognitive behavioral group therapy (CBGT) with respect to outcome.
Jastrowski, 2013[90]	6 patients	The primary purpose of the present study was to examine the feasibility, acceptability, and effectiveness of MBSR for a treatment-seeking sample of youth with chronic pain.
Field, 2013[91]	92 patients	The purpose of this study was to compare the effects of yoga (physical activity) versus social support (verbal activity) on prenatal and postpartum depression.
Lo, 2013[92]	82 patients	To explore the effects of Compassion-Mindfulness Therapy (C-MT) among patients depressive and anxiety
Hoge, 2013[93]	93 patients	This is the first randomized, controlled trial comparing the manualized Mindfulness-Based Stress Reduction (MBSR) program with an active control for generalized anxiety disorder (GAD), a disorder characterized by chronic worry and physiologic hyperarousal symptoms.
Pinniger, 2012[94]	97 patients	To determine whether tango dancing is as effective as mindfulness meditation in reducing symptoms of psychological stress, anxiety and depression, and in promoting well-being.
Manicavasagar, 2012[95]	69 patients	The aim of this study was to examine how rumination and mindfulness impact on treatment outcome in two group-based interventions for non-melancholic depression: Cognitive Behaviour Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT).
Ebnezar, 2012[32]	250 patients	To study the effect of integrated yoga on pain, morning stiffness and anxiety in osteoarthritis of knees.
Asmaee Majid, 2012[96]	31 patients	The aim of this study was to evaluate whether an eight-week group mindfulness-based stress reduction program would be an acceptable and effective treatment for patients suffering from GAD.
Tilbrook, 2011[97]	313 patients	To compare the effectiveness of yoga and usual care for chronic or recurrent low back pain.
Hall, 2011[98]	160 patients	To determine the effect of tai chi exercise on persistent low back pain.
Wong, 2011[99]	99 patients	Our objective was to compare the clinical effectiveness of the MBSR program with a multidisciplinary pain intervention (MPI) program in terms of pain intensity, pain-related distress, quality of life, and mood in patients with chronic pain.

Study	N	Objective
Vollestad, 2011[100]	76 patients	The aim of this study was to investigate the effect of mindfulness-based stress reduction (MBSR) for patients with heterogeneous anxiety disorders.
Schmidt, 2011[101]	177 patients	Efficacy of MBSR for enhanced well-being of fibromyalgia patients was investigated in a 3-armed trial
Segal, 2010[102]	160 patients	To compare rates of relapse in depressed patients in remission receiving MBCT against maintenance antidepressant pharmacotherapy, the current standard of care.
Godfrin, 2010[103]	106 patients	In this randomized controlled trial, the authors investigated the effects of MBCT on the relapse in depression and the time to first relapse since study participation, as well as on several mood states and the quality of life of the patients.
Britton, 2010[104]	26 patients	To examine whether mindfulness meditation (MM) was associated with changes in objectively measured polysomnographic (PSG) sleep profiles and to relate changes in PSG sleep to subjectively reported changes in sleep and depression within the context of a randomized controlled trial.
McCracken, 2013[105]	73 patients	The current study was designed to pilot test a brief, widely inclusive, local access format of ACT in a UK primary care setting.
Cohort Studies		
Serpa, 2014[12]	79 patients	To assess the impact of MBSR on Anxiety, depression, and pain among veterans
Gardiner, 2014[106]	65 patients	The primary goal of this study is to evaluate the feasibility of the integrative medical group visit (IMGV) care model in an inner-city racially diverse outpatient clinic. IMGV combines patient-centered, non-pharmacologic strategies and principles of mindfulness-based stress-reduction with a group medical visit to reduce pain and associated symptoms.
Munshi, 2013[107]	18 patients	This current investigation is unique in evaluating the long-term outcome of individuals with active depression who achieved remission with MBCT.
Idusohan-Moizer, 2013[108]	15 patients	This paper aims to evaluate the efficacy of an innovative structured mindfulness-based cognitive therapy (MBCT) group programme adapted for adults with ID with a diagnosis of either recurrent depression, anxiety or both clinical conditions and a history of deliberate self-harm behaviour.
Case-Control Studies		
None	–	–
Other		
Non-randomized trial Dimidjian, 2014[109]	49 patients	We examined the feasibility, acceptability, and clinical outcomes of depression symptom severity and relapse/recurrence associated with MBCT adapted for perinatal women (MBCT-PD).
Uncontrolled pilot (one arm) Goodman, 2014[13]	24 patients	This study examined the feasibility, acceptability, and clinical outcomes of the Coping with Anxiety through Living Mindfully (CALM) Pregnancy intervention.

Study	N	Objective
Non-randomized trial Shikatani, 2014[110]	56 patients	The current study examined the efficacy of a single session cognitive restructuring or mindfulness strategy on decreasing Postevent processing (PEP; reviewing a past social event in detail) and its associated effects, and investigated the cognitive processes involved.
Non-randomized trial Fish, 2014[111]	26 patients	This study explores the impact of a Mindfulness-Based Cancer Stress Management programme on psychological distress and quality of life.
Uncontrolled trial (one-arm pilot) Ljotsson, 2014[112]	41 patients	This study evaluated the efficacy, acceptability, and the health economic effects of an Internet-delivered acceptance and values-based exposure treatment for fibromyalgia
Uncontrolled pilot trial Schutze, 2014[113]	16 patients	This pilot study investigated the feasibility and clinical utility of implementing a novel, evidence-informed, interdisciplinary group intervention-Mindfulness Based Functional Therapy (MBFT)-for the management of persistent low back pain (LBP) in primary care.
Case study Foulk, 2014[114]	NR	An 8-week mindfulness-based cognitive therapy (MBCT) group for older adults with depression and/or anxiety is described. This article is based on an exploratory study of this therapeutic approach and changes in participants' symptoms associated with participation.
Uncontrolled pilot trial Kinser, 2014[115]	NR	The goal of our research study was to evaluate the feasibility, acceptability, and effects of a yoga intervention for women with MDD using standardized outcome measures and a long follow-up period (1year after the intervention).
Non-randomized trial Evans, 2013[42]	26 patients	The aim of this study was to assess the impact of a 6-week twice/week Iyengar yoga program on HRQoL of young adults with rheumatoid arthritis compared with a usual-care waitlist control group.
Non-randomized trial Do Rosario, 2013[116]	110 patients	The aim of the present study was to assess the efficiency of a single session of two modified Yoga positions with 110 subjects and their 147 pain-related complaints.
Non-randomized trial Ives-Deliperi, 2013[117]	23 patients	To explore if mindfulness-based cognitive therapy improves anxiety and depressive symptoms in bipolar disorder.
Uncontrolled pilot King, 2013[118]	20 patients	This study aimed to examine the impact of quantity of mindfulness meditation practice on the outcome of psychiatric symptoms following Mindfulness-based Cognitive Therapy (MBCT) for those diagnosed with bipolar disorder.
Non-randomized trial Naveen, 2013[43]	NR	To assess the impact of yoga either alone or with antidepressants on depression among Non-suicidal, consecutive out-patients of depression
Pooled data of both arms of an RCT Cramer, 2013[119]	51 patients	To assess the effects of a 9-week yoga intervention on chronic nonspecific neck pain 12 months after completion.
Non-randomized trial Delui, 2013[120]	45 patients	The aim of this study was to determine the effectiveness of rehabilitation techniques in cardiac patients including psychological-physical interventions such as Meditation and Relaxation.
Uncontrolled pilot trial Bedard, 2012[121]	23 patients	To demonstrate the efficacy of MBCT in the treatment of clinically diagnosed depression in a TBI population.

Study	N	Objective
Non-randomized trial Rungreangkulkij, 2011[122]	64 patients	The objective of this study was to assess the effect of Buddhist group therapy on patients with type 2 diabetes who had depressive symptoms.
Uncontrolled pilot Rosenthal, 2011[123]	5 patients	We conducted an uncontrolled pilot study to determine whether transcendental meditation (TM) might be helpful in treating veterans from Operation Enduring Freedom or Operation Iraqi Freedom with combat-related posttraumatic stress disorder (PTSD).
Uncontrolled pilot trial Stankovic, 2011[124]	15 patients	This eight-week study examined the feasibility of offering weekly classes in Integrative Restoration (iRest), a form of mindfulness meditation, to military combat veterans at a community mental health agency
Uncontrolled pilot trial Teixeira, 2010[125]	10 patients	This pilot study explored the effect of mindfulness meditation for diabetic neuropathy.
Non randomized trial Descilo, 2010[46]	183 patients	This study evaluated the effect of a yoga breath program alone and followed by a trauma reduction exposure technique on post-traumatic stress disorder and depression in survivors of the 2004 Asian tsunami.
Ongoing Studies (ClinicalTrials.gov)		
Yoga and Qigong for Elderly Patients With Chronic Low Back Pain (NCT01303588)	176 patients	Completed (December 2012). The objective of this study is to evaluate whether yoga or qigong therapy is effective in treating low back pain in elderly patients compared to no therapy (waiting list control). The secondary aim is to compare yoga and qigong.
Comparison of CAM and Conventional Mind-Body Therapies for Chronic Back Pain (NCT01467843)	297 patients	Ongoing (estimated completion September 2015). This trial will evaluate the effectiveness, and cost-effectiveness, of a safe and relatively inexpensive “mind-body” therapy that has the potential to provide relief to some of the millions of Americans who continue to suffer from chronic back pain.
KIDNET vs Meditation/Relaxation - a Dissemination Randomized Controlled Trial for the Treatment of Traumatized Children After War in Sri Lanka (NCT00564317)	48 patients	Completed (January 2006). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children when applied by locally trained teacher counsellors as well as the effectiveness and adequacy of such a treatment in a south-asian war affected stayee child community.
KIDNET Versus Meditation/Relaxation - a Dissemination RCTT for Children in Sri Lanka Traumatized by the War and the Tsunami (NCT00820391)	31 patients	Completed (October 2005). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children in Sri Lanka when applied by locally trained teacher counsellors.
Portable Mantram Meditation for Veterans With Military Related Post Traumatic Stress Syndrome (PTSD) (NCT01506323)	189 patients	Ongoing (estimated completion December 2014). The aim of this study is to determine the usefulness of a portable, meditation-based intervention called the Mantram Repetition Program (MRP) for Veterans with military-related posttraumatic stress disorder (PTSD).

Study	N	Objective
Dismantling Mindfulness (NCT01831362)	105 patients	Ongoing (estimated completion March 2016). The purpose of this study is to assess the clinical efficacy and mechanism of action of 2 component practices of "mindfulness meditation", i.e. focused awareness (FA) and open monitoring (OM) in comparison to each other and to the standard package, Mindfulness-Based Cognitive Therapy (MBCT).
The Effects and Mechanisms of Mindfulness Based Cognitive Therapy (MBCT) on Depressive Symptoms and Depression Relapse (NCT01145872)	92 patients	Completed (April 2013). This research proposal is intended to elucidate the efficacy and mechanisms underlying Mindfulness Based Cognitive Therapy (MBCT) in a population in remission from recurrent Major Depressive Disorder (MDD). The first objective of the study is to replicate previous studies' findings of MBCT's effects on decreasing depressive symptoms and depression relapse rates.
Yoga Breath Program and Client-Centered Exposure for Relief of PTSD in Tsunami Victims (NCT00290225)	180 patients	Completed (December 2005). Study hypothesis: that a standardized course of Eastern practices (Breath Water Sound Course -BWS) will significantly relieve PTSD and depression in tsunami victims. Further, that a client-centered exposure treatment (Traumatic Incident Reduction- TIR) would provide additional, significant relief of PTSD and depression in tsunami victims.
Feasibility of Mindfulness Meditation for Adults 65+ With Chronic Low Back Pain (NCT00594243)	37 patients	Completed (June 2005). We expect mindfulness meditation will result in a moderate effect size difference (0.5) between the intervention participants and wait-list control participants on outcome measures of pain, mood, physical function, attention, and QOL.
Loving-Kindness Meditation for PTSD (NCT01962714)	170 patients	Ongoing (estimated completion December 2017). This randomized controlled trial will assess whether a novel CAM intervention, Loving-kindness Meditation (LKM), is not meaningfully inferior to another group-based PTSD treatment, Cognitive Processing Therapy (Cognitive Only version; CPT-C) for reductions in PTSD and depressive symptoms.
Reducing Residual Depressive Symptoms With Web-based Mindful Mood Balance (NCT02190968)	460 patients	Ongoing (estimated completion December 2018). The investigators now propose a controlled study to determine whether MMB is more effective than usual care at reducing RDS and other key outcomes. If successful, MMB's online delivery format would provide high fidelity and low-cost empirically supported management of residual symptoms, leading to more robust remission, improved functioning and sustained recovery from MDD over time.
Preventing Depression Relapse With Mindfulness-Based Cognitive Therapy (NCT00183560)	184 patients	Completed (October 2010). This study will determine the effectiveness of mindfulness-based cognitive therapy (MBCT) in preventing depression relapse.

Study	N	Objective
Stress Reduction Techniques and Anxiety: Therapeutic and Neuroendocrine Effects (NCT01033851)	89 patients	Completed (February 2013). This study measures the efficacy of two different approaches to reducing anxiety and stress. One approach uses education, nutrition, exercise, and time management training, and another uses mindfulness meditation and yoga, which is taught as part of the Mindfulness-based stress reduction (MBSR) course, an 8-week manualized mindfulness intervention. We hypothesize that the two approaches will reduce anxiety in individuals with GAD in different ways. We will measure changes in stress hormones associated with these changes.
Meditation and Hypnosis for Chronic Depressed Mood (NCT00226863)	NR	Completed (September 2005). This study examined whether meditation or group psychotherapy including hypnosis plus education, compared to an educational control, would ameliorate long-term depressed mood.

Abbreviations not defined above: ACT=Acceptance and Commitment Therapy; BPSD=Bipolar Spectrum Disorder; CAM=Complementary/Alternative Medicine; GAD=Generalized Anxiety Disorder; HRQoL=Health Related Quality of Life; ID=intellectual disabilities; KIDNET=Kid Narrative Exposure Therapy; MABIs=Mindfulness and Acceptance Based Interventions; MBCT=Mindfulness Based Cognitive Therapy; MBCT-PD=Mindfulness Based Cognitive Therapy-Perinatal Depression; MBIs=Mindfulness Based Interventions; MBSR=Mindfulness Based Stress Reduction; MDD=Major Depressive Disorder; MMB=Mindful Mood Balance; N=number of studies/patients; NR=not reported; PTSD=Post Traumatic Stress Disorder; QOL=Quality of Life; RCTs=randomized controlled trials; RCTT=Randomized Controlled Treatment Trial; RDS=Residual Depressive Symptoms; SAD=Seasonal Affective Disorder; TBI=Traumatic Brain Injury; VA=Veterans Affairs

Appendix Table B-5. Published and ongoing studies potentially relevant to Research Question 5
[Does mindfulness-based interventions have equivalent safety and effectiveness compared with standard care for depression, anxiety, or pain?]

Study	N	Objective
Systematic Reviews		
Goyal, 2014[55]	41 studies	We aimed to determine the efficacy and safety of meditation programs on stress-related outcomes (e.g., anxiety, depression, stress, distress, well-being, positive mood, quality of life, attention, health-related behaviors affected by stress, pain, and weight) compared with an active control in diverse adult clinical populations
Hill, 2013[61]	4 studies	To assess randomized-control trials (RCTs) to ascertain whether yoga is an effective treatment in the management of patients with chronic low back pain (cLBP) compared with other care modalities.
Cramer, 2013[18]	10 studies	To systematically review and meta-analyze the effectiveness of yoga for low back pain.
Wang, 2013[19]	12 studies	To evaluate clinical trial evidence of the effectiveness of qigong exercise on depressive and anxiety symptoms
Oh, 2013[20]	10 studies	To evaluate the effects of Qigong on depression.
Wang, 2013[126]	15 studies	This study systematically reviewed the effects of Qigong on anxiety, depression, and psychological well-being.
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
Chen, 2012[21]	36 studies	No review has focused on the efficacy of meditation for anxiety specifically.
Balasubramaniam, 2012[7]	16 studies	To systematically examine the evidence for efficacy of yoga in the treatment of selected major psychiatric disorders.
Posadzki, 2011[23]	7 studies	To assess the effectiveness of yoga as a treatment option for low back pain
RCTs		
Sundquist, 2014[127]	215 patients	The aim of this randomised controlled trial (RCT) was to compare mindfulness-based group therapy with treatment as usual (primarily individual-based CBT) in primary care patients with depressive, anxiety or stress and adjustment disorders.
Prakhinkit, 2014[128]	45 patients	The objectives of this study were to determine the effects of the novel Buddhism-based walking meditation (BWM) and the traditional walking exercise (TWE) on depression, functional fitness, and vascular reactivity.
Williams, 2014[129]	274 patients	We compared mindfulness-based cognitive therapy (MBCT) with both cognitive psychological education (CPE) and treatment as usual (TAU) in preventing relapse to major depressive disorder (MDD) in people currently in remission following at least 3 previous episodes.
Ly, 2014[82]	81 patients	To evaluate and compare the effectiveness of two smartphone-delivered treatments: one based on behavioural activation (BA) and other on mindfulness.
Donald, 2014[83]	45 patients	The present study aimed to investigate the efficacy of Attention Training in comparison to an established treatment for social phobia, Cognitive Therapy.

Study	N	Objective
Kocovski, 2013[89]	137 patients	The purpose of the present study was to compare mindfulness and acceptance-based group therapy (MAGT) with cognitive behavioral group therapy (CBGT) with respect to outcome.
Hayes-Skelton, 2013[130]	81 patients	To examine whether an empirically and theoretically derived treatment combining mindfulness- and acceptance-based strategies with behavioral approaches would improve outcomes in generalized anxiety disorder (GAD) over an empirically supported treatment.
Arch, 2013[131]	71 patients	The current study examined three putative moderators of principal anxiety disorder severity outcomes for adapted mindfulness based stress reduction (MBSR) and group CBT - baseline depression symptoms, anxiety sensitivity, and diagnostic severity.
Arch, 2013[10]	105 patients	To compare a mindfulness-based intervention with cognitive behavioral therapy (CBT) for the group treatment of anxiety disorders
Cramer, 2013[132]	51 patients	To evaluate the effect of Iyengar yoga compared with exercise on chronic nonspecific neck pain.
Omidi, 2013[11]	90 patients	To evaluate efficacy of Mindfulness Based Cognitive Therapy (MBCT) and traditional Cognitive Behavior Therapy (CBT) with Treatments as usual (TAU) to reduce psychiatric symptoms in a sample of patients with Major Depressive Disorder (MDD)
Chiesa, 2012[133]	16 patients	To compare mindfulness-based cognitive therapy (MBCT) with a psycho-educational control group designed to be structurally equivalent to the MBCT program but excluding the claimed “active ingredient” of MBCT
Jazaieri, 2012[134]	56 patients	Mindfulness-based stress reduction (MBSR) is one nontraditional treatment that has demonstrated efficacy in treating other mood and anxiety disorders, and preliminary data suggest its efficacy in SAD as well.
Tekur, 2012[135]	80 patients	This study evaluated changes in pain, anxiety, depression and spinal mobility for CLBP patients on short-term, residential Yoga and physical exercise programs, including comprehensive yoga lifestyle modifications.
Manicavasagar, 2012[95]	69 patients	The aim of this study was to examine how rumination and mindfulness impact on treatment outcome in two group-based interventions for non-melancholic depression: Cognitive Behaviour Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT).
Sherman, 2011[33]	228 patients	To determine whether yoga is more effective than conventional stretching exercises or a self-care book for primary care patients with chronic low back pain
Wong, 2011[99]	99 patients	Our objective was to compare the clinical effectiveness of the MBSR program with a multidisciplinary pain intervention (MPI) program in terms of pain intensity, pain-related distress, quality of life, and mood in patients with chronic pain.
Manicavasgar, 2011[136]	45 patients	To examine the comparative effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) and Cognitive Behaviour Therapy (CBT) as treatments for non-melancholic depression.

Study	N	Objective
Segal, 2010[102]	160 patients	To compare rates of relapse in depressed patients in remission receiving MBCT against maintenance antidepressant pharmacotherapy, the current standard of care.
Esmer, 2010[37]	25 patients	To evaluate short-term efficacy of MBSR therapy for improving quality of life in adults with failed back surgery syndrome (FBSS)
Cohort Studies		
None	–	–
Case-Control Studies		
None	–	–
Other		
Non-randomized trial Naveen, 2013[43]	NR	To assess the impact of yoga either alone or with antidepressants on depression among non-suicidal, consecutive out-patients of depression
Non-randomized trial Gangadhar, 2013[14]	137 patients	The study was aimed to compare the therapeutic effect of a generic yoga module with antidepressant drugs in non-suicidal out-patients of major depression attending a psychiatric hospital.
Ongoing Studies (ClinicalTrials.gov)		
Comparison of CAM and Conventional Mind-Body Therapies for Chronic Back Pain (NCT01467843)	297 patients	Ongoing (estimated completion September 2015). This trial will evaluate the effectiveness, and cost-effectiveness, of a safe and relatively inexpensive "mind-body" therapy that has the potential to provide relief to some of the millions of Americans who continue to suffer from chronic back pain.
Loving-Kindness Meditation for PTSD (NCT01962714)	170 patients	Ongoing (estimated completion December 2017). This randomized controlled trial will assess whether a novel CAM intervention, Loving-kindness Meditation (LKM), is not meaningfully inferior to another group-based PTSD treatment, Cognitive Processing Therapy (Cognitive Only version; CPT-C) for reductions in PTSD and depressive symptoms.
Reducing Residual Depressive Symptoms With Web-based Mindful Mood Balance (NCT02190968)	460 patients	Ongoing (estimated completion December 2018). The investigators now propose a controlled study to determine whether MMB is more effective than usual care at reducing RDS and other key outcomes. If successful, MMB's online delivery format would provide high fidelity and low-cost empirically supported management of residual symptoms, leading to more robust remission, improved functioning and sustained recovery from MDD over time.
Preventing Depression Relapse With Mindfulness-Based Cognitive Therapy (NCT00183560)	184 patients	Completed (October 2010). This study will determine the effectiveness of mindfulness-based cognitive therapy (MBCT) in preventing depression relapse.

Abbreviations not defined above: CAM=Complementary/Alternative Medicine; CBT=Cognitive Behavior Therapy; CLBP=Chronic Lower Back Pain; MABIs=Mindfulness and Acceptance Based Interventions; MBCT=Mindfulness Based Cognitive Therapy; MBSR=Mindfulness Based Stress Reduction; MDD=Major Depressive Disorder; MMB=Mindful Mood Balance; N=number of studies/patients; NR=not reported; PTSD=Post Traumatic Stress Disorder; RCTs=randomized controlled trials; RDS=Residual Depressive Symptoms; SAD=Social Anxiety Disorder

Appendix Table B-6. Published and ongoing studies potentially relevant to Research Question 6
[What is the comparative safety and effectiveness of mindfulness-based interventions compared to other commonly used strategies (both pharmacologic and non-pharmacological)?]

Study	N	Objective
Systematic Reviews		
Goyal, 2014[55]	41 studies	We aimed to determine the efficacy and safety of meditation programs on stress-related outcomes (e.g., anxiety, depression, stress, distress, well-being, positive mood, quality of life, attention, health-related behaviors affected by stress, pain, and weight) compared with an active control in diverse adult clinical populations
Chugh-Gupta, 2013[4]	25 studies	The aim was to systematically review the evidence concerning the effectiveness of yoga as a treatment approach for state anxiety.
Hill, 2013[61]	4 studies	To assess randomized-control trials (RCTs) to ascertain whether yoga is an effective treatment in the management of patients with chronic low back pain (cLBP) compared with other care modalities.
Cramer, 2013[18]	10 studies	To systematically review and meta-analyze the effectiveness of yoga for low back pain.
Wang, 2013[19]	12 studies	To evaluate clinical trial evidence of the effectiveness of qigong exercise on depressive and anxiety symptoms
Oh, 2013[20]	10 studies	To evaluate the effects of Qigong on depression.
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
Chen, 2012[21]	36 studies	No review has focused on the efficacy of meditation for anxiety specifically.
Sarris, 2012[6]	NR	The objective of this metareview was to examine evidence across a broad range of CAM and lifestyle interventions in the treatment of anxiety disorders.
Balasubramaniam, 2012[7]	16 studies	To systematically examine the evidence for efficacy of yoga in the treatment of selected major psychiatric disorders.
Posadzki, 2011[23]	7 studies	To assess the effectiveness of yoga as a treatment option for low back pain
RCTs		
Tovote, 2014[75]	94 patients	The aim of this study was to assess the efficacy of individual mindfulness-based cognitive therapy (MBCT) and individual cognitive behavior therapy (CBT) in comparison with a waiting-list control condition for treating depressive symptoms in adults with type 1 or type 2 diabetes.
Prakhinkit, 2014[128]	45 patients	The objectives of this study were to determine the effects of the novel Buddhism-based walking meditation (BWM) and the traditional walking exercise (TWE) on depression, functional fitness, and vascular reactivity.
Williams, 2014[129]	274 patients	We compared mindfulness-based cognitive therapy (MBCT) with both cognitive psychological education (CPE) and treatment as usual (TAU) in preventing relapse to major depressive disorder (MDD) in people currently in remission following at least 3 previous episodes.
Ly, 2014[82]	81 patients	To evaluate and compare the effectiveness of two smartphone-delivered treatments: one based on behavioural activation (BA) and other on mindfulness.

Study	N	Objective
Kocovski, 2013[89]	137 patients	The purpose of the present study was to compare mindfulness and acceptance-based group therapy (MAGT) with cognitive behavioral group therapy (CBGT) with respect to outcome.
Field, 2013[91]	92 patients	The purpose of this study was to compare the effects of yoga (physical activity) versus social support (verbal activity) on prenatal and postpartum depression.
Hayes-Skelton, 2013[130]	81 patients	To examine whether an empirically and theoretically derived treatment combining mindfulness- and acceptance-based strategies with behavioral approaches would improve outcomes in generalized anxiety disorder (GAD) over an empirically supported treatment.
Arch, 2013[131]	71 patients	The current study examined three putative moderators of principal anxiety disorder severity outcomes for adapted mindfulness based stress reduction (MBSR) and group CBT - baseline depression symptoms, anxiety sensitivity, and diagnostic severity.
Omidi, 2013[11]	90 patients	To evaluate efficacy of Mindfulness Based Cognitive Therapy (MBCT) and traditional Cognitive Behavior Therapy (CBT) with Treatments as usual (TAU) to reduce psychiatric symptoms in a sample of patients with Major Depressive Disorder (MDD)
Chiesa, 2012[133]	16 patients	To compare mindfulness-based cognitive therapy (MBCT) with a psycho-educational control group designed to be structurally equivalent to the MBCT program but excluding the claimed “active ingredient” of MBCT
Jazaieri, 2012[134]	56 patients	Mindfulness-based stress reduction (MBSR) is one nontraditional treatment that has demonstrated efficacy in treating other mood and anxiety disorders, and preliminary data suggest its efficacy in SAD as well.
Tekur, 2012[135]	80 patients	This study evaluated changes in pain, anxiety, depression and spinal mobility for CLBP patients on short-term, residential Yoga and physical exercise programs, including comprehensive yoga lifestyle modifications.
Manicavasagar, 2012[95]	69 patients	The aim of this study was to examine how rumination and mindfulness impact on treatment outcome in two group-based interventions for non-melancholic depression: Cognitive Behaviour Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT).
Sherman, 2011[33]	228 patients	To determine whether yoga is more effective than conventional stretching exercises or a self-care book for primary care patients with chronic low back pain
Wong, 2011[99]	99 patients	Our objective was to compare the clinical effectiveness of the MBSR program with a multidisciplinary pain intervention (MPI) program in terms of pain intensity, pain-related distress, quality of life, and mood in patients with chronic pain.
Manicavasgar, 2011[136]	45 patients	To examine the comparative effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) and Cognitive Behaviour Therapy (CBT) as treatments for non-melancholic depression.
Segal, 2010[102]	160 patients	To compare rates of relapse in depressed patients in remission receiving MBCT against maintenance antidepressant pharmacotherapy, the current standard of care.

Study	N	Objective
Esmer, 2010[37]	25 patients	To evaluate short-term efficacy of MBSR therapy for improving quality of life in adults with failed back surgery syndrome (FBSS)
Cohort Studies		
None	–	–
Case-Control Studies		
Dimidjian, 2014[137]	100 patients	The present study examined Mindful Mood Balance (MMB), the first web-based approach to deliver the core content of MBCT with recurrently depressed individuals
Other		
Non-randomized trial Gangadhar, 2013[14]	137 patients	The study was aimed to compare the therapeutic effect of a generic yoga module with antidepressant drugs in non-suicidal out-patients of major depression attending a psychiatric hospital.
Ongoing Studies (ClinicalTrials.gov)		
Ai Chi Versus Stretching in Fibromyalgia Management (NCT00600574)	94 patients	Completed (February 2008). The purpose of the study is to compare the efficacy and tolerability of Ai Chi, an adaptation of Tai Chi exercise to water, with stretching on fibromyalgia symtomatology.
Comparison of CAM and Conventional Mind-Body Therapies for Chronic Back Pain (NCT01467843)	297 patients	Ongoing (estimated completion September 2015). This trial will evaluate the effectiveness, and cost-effectiveness, of a safe and relatively inexpensive “mind-body” therapy that has the potential to provide relief to some of the millions of Americans who continue to suffer from chronic back pain.
KIDNET vs Meditation/Relaxation - a Dissemination Randomized Controlled Trial for the Treatment of Traumatized Children After War in Sri Lanka (NCT00564317)	48 patients	Completed (January 2006). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children when applied by locally trained teacher counsellors as well as the effectiveness and adequacy of such a treatment in a south-asian war affected stayee child community.
KIDNET Versus Meditation/Relaxation - a Dissemination RCTT for Children in Sri Lanka Traumatized by the War and the Tsunami (NCT00820391)	31 patients	Completed (October 2005). The purpose of this study is to assess the efficacy of KIDNET versus a Meditation/Relaxation protocol in treating traumatized children in Sri Lanka when applied by locally trained teacher counsellors.
Reducing Residual Depressive Symptoms With Web-based Mindful Mood Balance (NCT02190968)	460 patients	Ongoing (estimated completion December 2018). The investigators now propose a controlled study to determine whether MMB is more effective than usual care at reducing RDS and other key outcomes. If successful, MMB’s online delivery format would provide high fidelity and low-cost empirically supported management of residual symptoms, leading to more robust remission, improved functioning and sustained recovery from MDD over time.

Study	N	Objective
Preventing Depression Relapse With Mindfulness-Based Cognitive Therapy (NCT00183560)	184 patients	Completed (October 2010). This study will determine the effectiveness of mindfulness-based cognitive therapy (MBCT) in preventing depression relapse.
Stress Reduction Techniques and Anxiety: Therapeutic and Neuroendocrine Effects (NCT01033851)	89 patients	Completed (February 2013). This study measures the efficacy of two different approaches to reducing anxiety and stress. One approach uses education, nutrition, exercise, and time management training, and another uses mindfulness meditation and yoga, which is taught as part of the Mindfulness-based stress reduction (MBSR) course, an 8-week manualized mindfulness intervention. We hypothesize that the two approaches will reduce anxiety in individuals with GAD in different ways. We will measure changes in stress hormones associated with these changes.
Meditation and Hypnosis for Chronic Depressed Mood (NCT00226863)	NR	Completed (September 2005). This study examined whether meditation or group psychotherapy including hypnosis plus education, compared to an educational control, would ameliorate long-term depressed mood.

Abbreviations not defined above: CAM=Complementary/Alternative Medicine; CBT=Cognitive Based Therapy; CLBP=Chronic Lower Back Pain; GAD=Generalized Anxiety Disorder; KIDNET=Kid Narrative Exposure Therapy; MABIs=Mindfulness and Acceptance Based Therapy; MBCT=Mindfulness Based Cognitive Therapy; MBSR=Mindfulness Based Stress Reduction; MMB=Mindful Mood Balance; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials; RCTT=Randomized Controlled Treatment Trial; RDS=Residual Depressive Symptoms; SAD=Social Anxiety Disorder

Appendix Table B-7. Published and ongoing studies potentially relevant to Research Question 7

[Does the comparative effectiveness of mindfulness-based interventions for depression, anxiety, or pain differ by method of delivery/patient practice (self-help, phone-based, or Internet-based, expert-led group vs self/home practice)?]

Study	N	Objective
Systematic Reviews		
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
RCTs		
Thompson, 2014[70]	128 patients	This study evaluated the efficacy of a mindfulness-based cognitive therapy intervention for preventing major depressive disorder (MDD) episodes in people with epilepsy.
Morgan, 2014[87]	NR	The current study examined the relationships between separate single item measurements of three types of mindfulness practices (formal, informal, and mindfulness of breath in daily life) and longer-term outcomes in worry, clinician-rated anxiety severity, and quality of life following treatment with an acceptance-based behavior therapy (ABBT) for Generalized Anxiety Disorder (GAD) in two separate treatment studies.
Cohort Studies		
Groessl 2012[138]	53 patients	The purpose of this study was to assess the impact of a yoga intervention on women and men with CLBP
Case-Control Studies		
None	–	–

Study	N	Objective
Other		
None	–	–
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: CLBP=Chronic Lower Back Pain; MABIs=Mindfulness and Acceptance Based Interventions; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

Appendix Table B-8. Published and ongoing studies potentially relevant to Research Question 8

[Does the comparative effectiveness of mindfulness-based strategies for depression, anxiety, or pain differ by dose and frequency of treatment (e.g., length, intensity, frequency, or number of sessions, addition of booster sessions)?]

Study	N	Objective
Systematic Reviews		
Vollestad, 2012[5]	19 studies	To review and synthesize extant research on MABIs for patients with diagnoses of anxiety disorders.
RCTs		
Crane, 2014[8]	99 patients	Few empirical studies have explored the associations between formal and informal mindfulness home practice and outcome in Mindfulness-based Cognitive Therapy (MBCT). In this study ninety-nine participants randomised to MBCT in a multi-centre randomised controlled trial completed self-reported ratings of home practice over 7 treatment weeks.
Ussher, 2014[81]	55 patients	MBSR typically entails an intensive 8-week intervention. The effects of very brief mindfulness interventions are unknown. Among those with chronic pain, the immediate effects of a 10 min mindfulness-based body scan were compared with a control intervention.
Cohort Studies		
Perich, 2013[139]	NR	This study aimed to examine the impact of quantity of mindfulness meditation practice on the outcome of psychiatric symptoms following Mindfulness-based Cognitive Therapy (MBCT) for those diagnosed with bipolar disorder.
Case-Control Studies		
None	–	–
Other		
Mix method (qual + Pre post followup surveys) Eyles, 2015[140]	19 patients	Mindfulness-based stress reduction (MBSR) can help self-management of anxiety, depression, quality of life (QoL), and fatigue and has been evaluated in early-stage breast cancer but not MBC. This study investigated the acceptability and feasibility of providing MBSR for women with MBC and of introducing MBSR into a National Health Service (NHS) setting.
Ongoing Studies (ClinicalTrials.gov)		
None	–	–

Abbreviations not defined above: MABIs=Mindfulness and Acceptance Based Interventions; MBC=Metastatic Breast Cancer; MBSR=Mindfulness Based Stress Reduction; N=number of studies/patients; NR=not reported; RCTs=randomized controlled trials

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