

A logic model for precision medicine implementation informed by stakeholder views and implementation science

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Purpose: Precision medicine promises to improve patient outcomes, but much is unknown about its adoption within health-care systems. A comprehensive implementation plan is needed to realize its benefits.

Methods: We convened 80 stakeholders for agenda setting to inform precision medicine policy, delivery, and research. Conference proceedings were audio-recorded, transcribed, and thematically analyzed. We mapped themes representing opportunities, challenges, and implementation strategies to a logic model, and two implementation science frameworks provided context.

Results: The logic model components included inputs: precision medicine infrastructure (clinical, research, and information technology), big data (from data sources to analytics), and resources (e.g., workforce and funding); activities: precision medicine research, practice, and education; outputs: precision medicine diagnosis; outcomes: personal utility, clinical utility, and health-care utilization; and impacts: precision medicine value, equity and access, and

economic indicators. Precision medicine implementation challenges include evidence gaps demonstrating precision medicine utility, an unprepared workforce, the need to improve precision medicine access and reduce variation, and uncertain impacts on health-care utilization. Opportunities include integrated health-care systems, partnerships, and data analytics to support clinical decisions. Examples of implementation strategies to promote precision medicine are: changing record systems, data warehousing techniques, centralized technical assistance, and engaging consumers.

Conclusion: We developed a theory-based, context-specific logic model that can be used by health-care organizations to facilitate precision medicine implementation.

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INTRODUCTION

Precision medicine considers individual differences and preferences to inform personalized health-care decisions that aim to improve health outcomes. Genomic medicine is fundamental to current precision medicine programs. Yet, many health-care systems have not systematically integrated genomic medicine into clinical care because of the complexity of genomic information, limited numbers of genetics professionals, lack of preparedness of most health-care professionals, and barriers to coverage and reimbursement.^{1–8} An optimal implementation plan in genomic medicine is crucial to realizing the benefits of precision medicine services delivered within health-care organizations. Other applications

of precision medicine, such as proteomics and metabolomics, will probably face similar challenges to adoption.

Like other health-care systems, the Veterans Health Administration (VHA) is considering how best to integrate research discoveries into clinical practice, and expand clinical genetic and genomic medicine services.⁹ The VHA has made a substantial investment in precision medicine, as evidenced by the establishment of the Million Veteran Program (a research program designed to study how genes affect health) and formation of the national Genomic Medicine Service (a centralized team of genetic counselors based in Salt Lake City who provide genetic services through telehealth service agreements). In addition, there are regional VHA clinical

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genetics programs based in Boston, Houston, and Los Angeles that provide genetic consultation on-site and via telehealth. To assist the VHA with precision medicine strategic planning, we convened key stakeholders for a one-day conference. The goal of the conference was to foster partnerships between key stakeholders for agenda setting to inform precision medicine policy, delivery, and research. We used the conference proceedings as a source of qualitative data to gather themes for the development of a logic model that could be used to inform precision medicine implementation in the VHA and other health-care organizations.

MATERIALS AND METHODS

Conference planning and participants

We invited participants from stakeholder groups identified as being critical to achieve the conference goal, including: patients, family members, and advocacy organizations; clinicians (primary care providers, geneticists, genetic counselors, and other medical specialists); researchers (basic science, health services, and implementation researchers, including information technology experts); policymakers and payers; and administrators and managers of VHA and non-VHA health-care organizations. We used purposive recruitment to achieve a diverse participant panel that would provide a comprehensive view of precision medicine within and outside the VHA. There were 90 invitees, about half of whom were affiliated with the VHA.

The conference was held on 25 August 2016 in Arlington, Virginia. Each of nine sessions comprised a panel of three to six speakers and time for an open discussion with the audience. Before the conference, session moderators emailed speakers three to four open-ended questions to inform their presentations. These questions addressed the benefits of (and opportunities for) precision medicine, challenges and barriers to precision medicine, and strategies that can promote precision medicine adoption and implementation. We used qualitative analysis of the conference proceedings to inform the development of a logic model, and applied implementation science frameworks to provide context and anchor themes that informed the model, as described below. The project was considered non-research by the Veterans Affairs Greater Los Angeles Healthcare System Institutional Review Board.

Research topics identified

At the conference, during the afternoon break, three program committee members (M.T.S., B.L., and J.P.) met with one of the invited speakers (E.M.Y.) to identify research topics addressed during the conference. This group identified nine research topics relevant to the planned thematic analysis: preclinical and clinical research; health services and outcomes research; dissemination and implementation research; organization and provider behavior research; partnered research; economics research; information technology and clinical informatics; public engagement; and ethics and equity.

Data collection and transcript coding

The conference proceedings were audio-recorded and professionally transcribed. Transcripts were reviewed and edited for accuracy. Thematic analysis of the transcripts was based on an iterative, consensus approach that included: establishment of a coding dictionary; independent dual coding of themes with comparison (C.C.-C. and M.T.S.); deliberation and resolution of discrepancies; and review by an auditor not involved in coding when resolution of coding discrepancies could not be reached (J.P.).

We used a matrix method to facilitate transcript coding. We listed speaker statements in the rows of the matrix and the nine research topics in the columns of the matrix. The coders matched each statement to a research topic and entered a theme into the intersecting cell of the matrix. When statements mapped to more than one research topic, the coders selected primary and secondary research topics. The primary research topic was used in the synthesis of findings. We also characterized each statement and associated theme as an opportunity, challenge, or strategy. We defined opportunities as existing activities and resources that could support precision medicine implementation, and challenges as any factor, objective, or subjective perceived by the stakeholders as a potential barrier to precision medicine implementation. For implementation strategies, we used the definition from Proctor and colleagues, “methods or techniques used to enhance the adoption, implementation and sustainability of a clinical program.”¹⁰ We excluded statements of casual conversations (e.g., transition between speakers), and those related to the speakers’ personal information or role in precision medicine.

Anchoring precision medicine themes to implementation science frameworks

Figure 1 illustrates the process we used for coding and mapping that resulted in a precision medicine implementation plan. Two coders (C.C.-C. and M.T.S.) independently mapped the themes identified to the W.K. Kellogg Foundation Logic Model components,¹¹ Consolidated Framework for Implementation Research (CFIR) constructs,¹² and Expert Recommendations for Implementing Change (ERIC) compilation of implementation strategies.¹³ Discrepancies were discussed and, when needed, adjudicated by a third investigator (J.P.).

The logic model consists of the planned work (inputs and activities) and intended results (outputs, outcomes, and impacts) for implementation of a program. We used the logic model component definitions, as described by the W.K. Kellogg Foundation. Inputs include the human, financial, organizational, and community resources available to do the work; activities include the processes and intentional actions to bring about the intended program results; outputs are the direct products of program activities; outcomes are changes in behavior, knowledge, skills, status, and level of functioning; and impact is the intended or unintended change occurring in

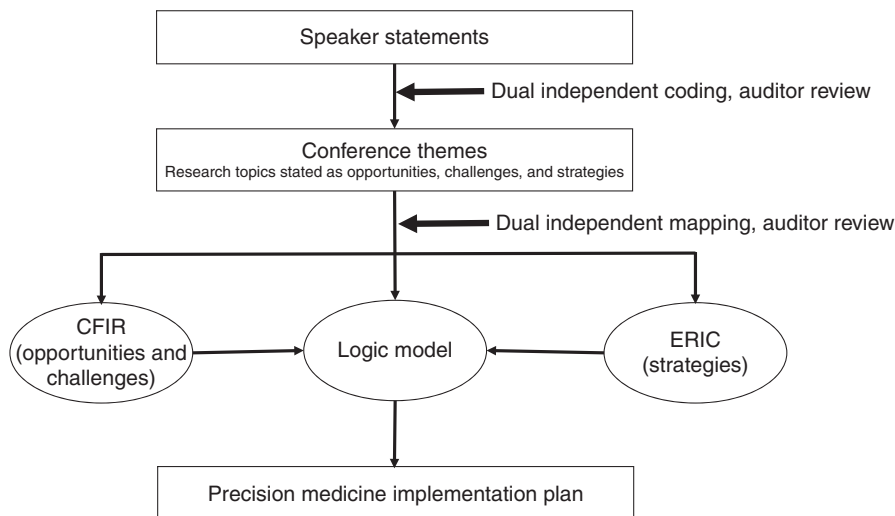


Fig. 1 Flow chart summarizing the coding and analysis of the conference proceedings. *CFIR* Consolidated Framework for Implementation Research, *ERIC* Expert Recommendations for Implementing Change.

organizations, communities, or systems as a result of the program activities.¹¹

We mapped themes stated as opportunities or challenges to the CFIR, as defined by Damschroder and colleagues.¹² The CFIR provides a menu of constructs that can be used as a practical guide for systematically assessing potential barriers and facilitators in preparation for implementing an innovation and providing theory-based constructs for developing context-specific logic models. The CFIR is composed of five major domains and its associated constructs: 8 constructs comprise the intervention characteristics domain (e.g., evidence strength and quality), 4 constructs comprise the outer setting domain (e.g., patient needs and resources), 12 constructs comprise the inner setting domain (e.g., culture and leadership engagement), 5 constructs comprise the individual characteristics domain, and 8 constructs comprise the process domain (e.g., plan, evaluate, and reflect). We chose the CFIR because it is easily customized to diverse settings and scenarios. By providing a framework of constructs, the CFIR promotes consistent use of constructs, systematic analysis, and organization of findings from implementation studies.¹² All CFIR domains are relevant to precision medicine implementation; however, for this study, the inner domain constructs are of particular interest given the focus on implementation within a health-care organization.

We mapped themes stated as strategies to the compilation of implementation strategies, as defined by the ERIC study.^{13–15} The ERIC compilation consists of 9 clusters of 73 implementation strategies, including: use evaluative and iterative strategies (e.g., audit and provide feedback, and develop and organize quality monitoring systems); provide interactive assistance (e.g., provide local technical assistance, and provide centralized technical assistance); adapt and tailor to context (e.g., use data experts and use data warehousing techniques); develop

stakeholder inter-relationships (e.g., use advisory boards and work groups, and identify early adopters); train and educate stakeholders (e.g., develop educational materials and conduct educational meetings); support clinicians (e.g., remind clinicians and facilitate relay of clinical data to providers); engage consumers (e.g., involve patients/consumers and family members); utilize financial strategies (e.g., access new funding and alter incentive/allowance structures); and change infrastructure (e.g., change record systems and change service sites). We chose the ERIC compilation because it is a comprehensive collection of implementation strategies developed by implementation science experts using a systematic approach to identify, develop, and evaluate a consistent language and description of implementation strategies.¹³

RESULTS

Eighty individuals attended the conference and 58 contributed to the discussion as speakers or audience members. We identified 419 discrete speaker statements. We excluded 116 statements describing participant background and experience with precision medicine. Among the remaining 303 statements, we identified 47 unique themes. We classified 82 (27%) statements as opportunities, 89 (29%) as challenges, and 132 (44%) as strategies.

A logic model for precision medicine implementation

A logic model for a precision medicine program within a health-care organization is shown in Figure 2. Assumptions underlying the logic model discussed during the conference included: precision medicine will improve health outcomes; precision medicine has value beyond clinical utility; and the confluence of clinical care and research is critical for successful precision medicine implementation. As we mapped the conference themes to the logic model components, higher-level concepts emerged, and we arranged the themes within

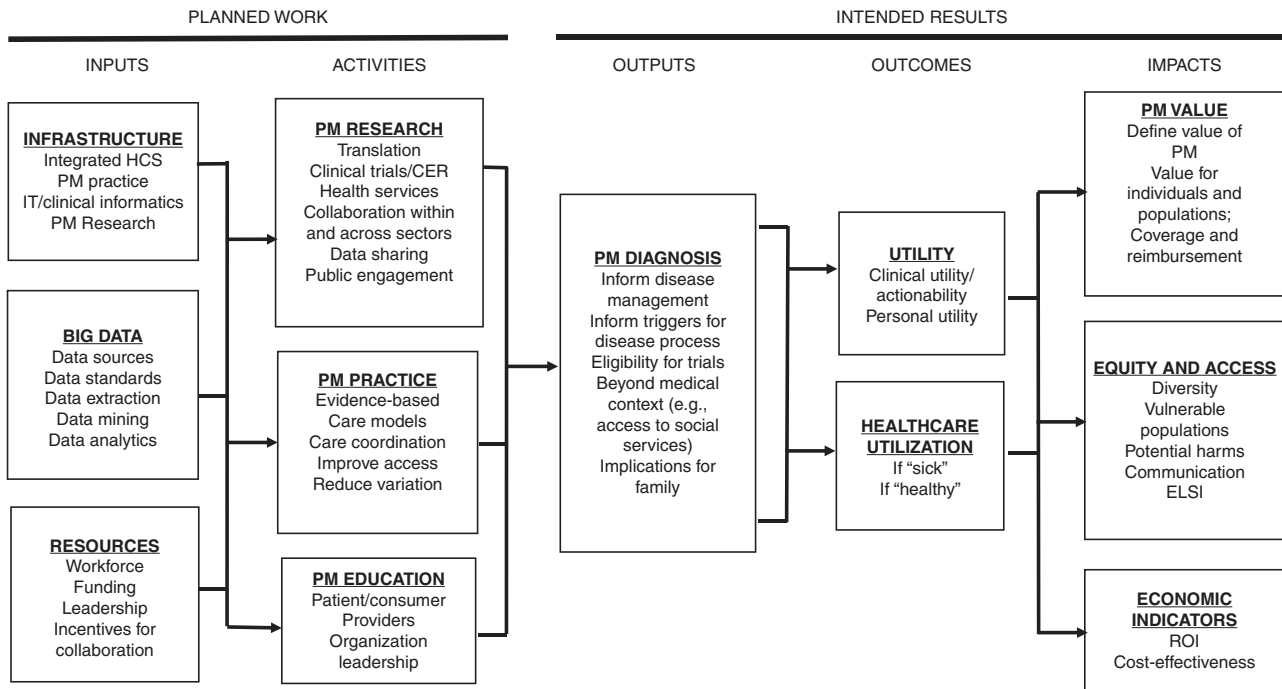


Fig. 2 Logic model for precision medicine implementation informed by key stakeholders. Concepts and associated themes identified from transcript coding of the conference proceedings were arranged into a logic model for precision medicine implementation. The logic model can be used by a health-care organization to inform the planned work (inputs and activities) and intended results (outputs, outcomes, and impact). Assumptions underlying the logic model include: precision medicine will improve health outcomes; precision medicine has value beyond clinical utility; and the confluence of clinical care and research is critical for successful precision medicine implementation. *IT* information technology, *PM* precision medicine, *CER* comparative effectiveness research, *ELSI* ethical, legal and social issues, *HCS* health-care system, *ROI* return on investment.

these concepts. For example, three concepts emerged for inputs: infrastructure, big data, and resources.

The contribution of the different stakeholder groups to the logic model concepts is shown in Figure 3. Individuals from every stakeholder group participated in the discussion. Individuals from multiple stakeholder groups contributed to the themes that mapped to every concept within the logic model, except for the health-care utilization concept within the outcomes component. In this instance, only clinicians contributed statements.

Research topic mapping to the logic model

Many of the conference discussions addressed the early stages of the logic model, with 73% of the themes mapping to inputs (e.g., big data) and activities (e.g., precision medicine practice and precision medicine research). The research topics of information technology and clinical informatics, outcomes research, and organization and provider behavior research predominated within the inputs component of the logic model, with most themes stated as opportunities. For the activities component, partnered research, dissemination and implementation research, and organization and provider behavior research were the most common, with partnered research most often stated as an opportunity, and dissemination and implementation research and organization and provider behavior research most often stated as a challenge or

strategy. The outcomes research topic predominated among statements mapping to the logic model components of outputs (most often stated as opportunities) and outcomes (most often stated as challenges). For the impact component of the logic model, the research topics of dissemination and implementation research, outcomes research, and ethics and equity were most common, and typically stated as challenges. Supplementary Table 1 shows the distribution of research topics for themes stated as opportunities, challenges, and strategies according to the logic model components and concepts.

Context for precision medicine planning: mapping CFIR constructs to the logic model

We mapped themes stated as opportunities or challenges to 24 CFIR constructs (Table 1). The logic model concept of precision medicine research, which had the greatest number of themes stated as opportunities for precision medicine (e.g., communication with stakeholders, partnerships within a health-care organization, and partnerships across sectors) mapped to the CFIR constructs of: evidence strength and quality, adaptability, cosmopolitanism (i.e., the degree to which an organization is networked with other external organizations), networks and communications, implementation climate, available resources, and planning. The logic model concept of equity and access had the greatest number of

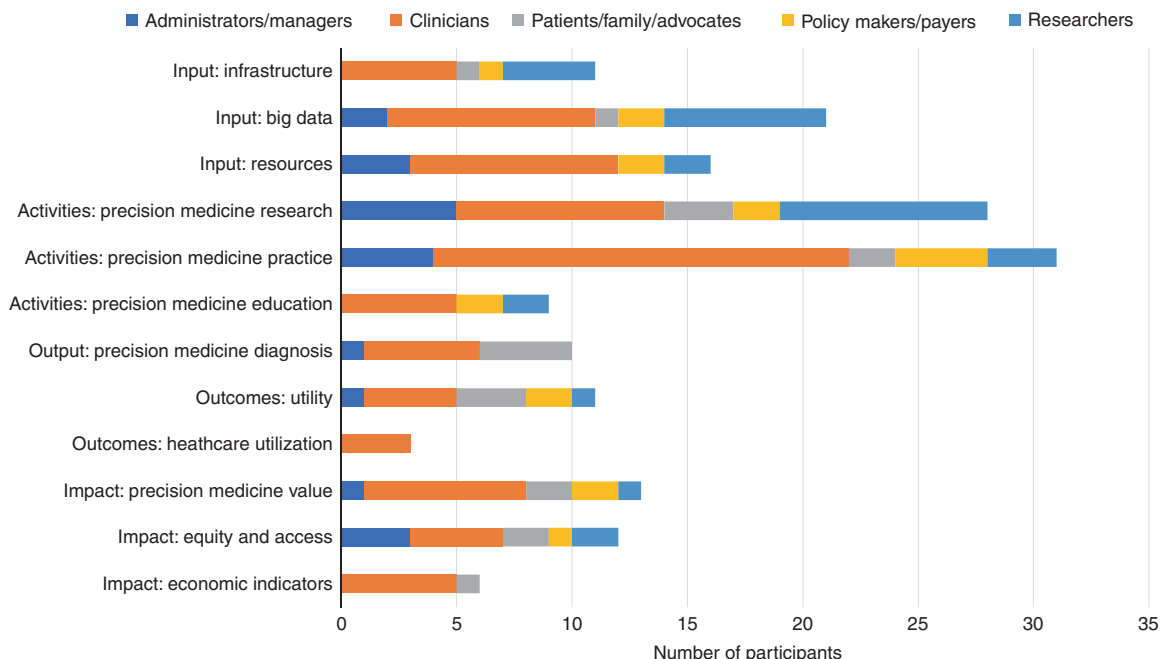


Fig. 3 Number of participants contributing to the logic model concepts by stakeholder group. Total number of participants by stakeholder group: administrators/managers: *n* = 11; clinicians: *n* = 22; patients/family/advocates: *n* = 6; policymakers/payers: *n* = 5; researchers: *n* = 13. One participant could not be identified in the transcript, and was therefore not featured here.

challenges for precision medicine (e.g., ethical, legal and social issues that limit precision medicine practice, such as return of genetic test results in the research setting, and individuals with rare genetic disorders being a vulnerable population) and mapped to the CFIR constructs of complexity, patient needs and resources, external policy and incentives, relative priority, access to knowledge and information, and knowledge and beliefs about the intervention.

Context for precision medicine planning: mapping ERIC implementation strategies to the logic model

We mapped themes representing strategies for precision medicine to 42 implementation strategies from all 9 clusters of the ERIC compilation (Table 2). The logic model concept of precision medicine practice had the greatest number of themes stated as strategies, whereas health-care utilization had none. Many strategies were related to information technology and clinical informatics to support clinical decision-making and reduce variation in precision medicine practice, such as changing record systems, using data warehousing techniques, developing and implementing tools for quality monitoring, and using centralized technical assistance. Other strategies focused on promoting communication and data sharing by developing partnerships, engaging consumers, and training and educating stakeholders. To improve access to precision medicine, conference participants described the use of financial strategies, changing service sites, creating new clinical teams, revising clinical roles, recruiting and training leadership, adapting and tailoring precision medicine interventions to context, and mandating policy changes.

DISCUSSION

We have developed a comprehensive logic model for precision medicine program planning that is grounded in implementation science and informed by deliberations of diverse stakeholder groups brought together for a conference focused on integration of precision medicine in clinical care. The use of the W.K. Kellogg Logic Model helped organize the themes and higher-level concepts described by conference participants. The logic model serves as a roadmap for precision medicine program planning and evaluation that links short- and long-term outcomes with inputs and activities.¹¹ We also used implementation science frameworks (the CFIR and ERIC compilation) to provide context for the logic model.^{12,13} This formalized approach provides a common set of constructs that are transferrable to any health-care organization considering precision medicine implementation, and is useful for standardizing investigations of precision medicine implementation studies. The mapping of CFIR domains and constructs to the precision medicine challenges and opportunities could be used as a checklist to help a health-care organization identify local factors likely to influence precision medicine implementation, and mapping of the ERIC implementation strategies to the precision medicine strategies could help with prioritizing strategies likely to enhance the adoption and implementation of precision medicine across the organization.

Planned work for precision medicine implementation (i.e., logic model inputs and activities) predominated the conference discussion, which suggests we are still early in the adoption of precision medicine. We learned that while

Table 1 Conference themes stated as opportunities or challenges mapped to CFIR and the logic model
Paraphrased statements

Paraphrased statements	Conference themes	CFIR constructs	CFIR domains
Logic model component: inputs; concept: infrastructure Developing robust genetic/genomic testing platforms	Precision medicine practice infrastructure Integrated health-care system	Design quality and packaging Structural Characteristics	Intervention characteristics Inner setting
Longitudinal follow-up is possible with integrated health-care systems; integrated health-care system can evaluate value of precision medicine; VHA well positioned to study precision medicine outcomes	Opportunity	"	"
Longitudinal EHR data available within VHA for research	Opportunity	"	"
In VHA, we are big and can leverage our size and economies of scale	Challenge	"	"
Human subjects review process is slow	Opportunity	Networks and communications	"
Mobile apps for patients and providers that interface with a data warehouse	Opportunity	"	"
Logic model component: inputs; concept: big data Data mining to inform outcomes research; genotype-phenotype associations	Data mining	Evidence strength and quality	Intervention characteristics
Gathering data to establish value for rare diseases; capturing relevant outcomes	Challenge	"	"
Integrated analytic products for both internal and external data	Opportunity	Design quality and packaging	"
Use RAND best practices for genetic test reporting	Opportunity	"	"
Keeping clinical and research data separate	Challenge	"	"
Data standards for representing genetic information in the EHR; research testing does not meet quality standards for clinical testing	Challenge	"	"
Extract high-quality, reliable phenotypic information from the EHR; getting structured data from genetic test results; automated data extraction from genetic test reports is still lacking	Challenge	"	"
Annotation of pharmacogenetics test reports; data integration/return of genetic test result in the EHR; format of genetic test reports makes interpretation difficult for most providers	Challenge	"	"
Data analytics to operationalize genetics referrals	Opportunity	"	"
Learning health-care system by leveraging data analytics; family history section in the EHR to promote predictive medicine; adapt current informatics tools to facilitate precision medicine practice (e.g., automatic risk assessment and referral to preventive services)	Opportunity	Networks and communications Access to knowledge and information	Inner setting
Capturing data and creating a learning health-care system	Opportunity	"	"
In VHA, VIREC helps locate and use VHA and non-VHA data (e.g., Medicare)	Opportunity	"	"
Develop registry to monitor precision medicine outcomes; informatics can help evaluate utilization of precision medicine services	Opportunity	Cosmopolitanism Reflecting and evaluating	Outer setting Process
Logic model component: inputs; concept: resources Ensure funding stream for qualified investigators; pay for genetic testing to ensure eligibility for clinical trial; cost of genetic testing limits its use; need resources to conduct CLIA-approved testing with the VHA MVP to allow return of results	Challenge	Cost	Intervention characteristics
The genomic workforce is insufficient to meet the demand for precision medicine; most providers are not prepared for precision medicine; the workforce on the frontline is not ready/they are not informed about when genetic tests should be ordered and how to interpret results; precision medicine expertise is limited	Challenge	Patient needs and resources	Intervention characteristics
Leadership making precision medicine a priority	Opportunity	Leadership engagement Available resources	Inner setting
Intersection of clinical care and research; engage and recruit the best and brightest clinician-scientists; Veterans Affairs Big Data Scientist Training Enhancement Program bridges gap between clinical world and operations	Opportunity	"	"
Incentives to promote collaboration	Opportunity	"	"
No clinical genetics expertise or access to genetic counseling after testing	Challenge	"	"
Funding needed to scale-up precision medicine practice	Challenge	"	"
Logic model component: activities; concept: precision medicine research Clinical trials are needed to get at outcomes; comparative effectiveness studies are needed; increase patient-reported outcomes research; develop metrics for personal utility	Opportunity	Evidence strength and quality	Intervention characteristics
Genomics is so dynamic; consider new design for implementation research that does not require a strong evidence base	Opportunity	"	"
N-of-1 trials; point-of-care clinical trial program	Opportunity	Adaptability Network and communications	Inner setting
Collaboration is promoted since we are all one big team in the VHA	Opportunity	"	"
Competitive environment impairs conducting research in collaborative way	Challenge	"	"
Story telling by patients about their precision medicine experience	Opportunity	Implementation climate	"
Veterans are altruistic and engaged; public as a source of data; public interest in genetics and participating in research; public interest in sharing genomic data	Opportunity	"	"
Enroll VHA patients in clinical trials	Opportunity	Available resources Cosmopolitanism	Outer setting
Collaboration across VHA offices provides data for VIREC—the VHA's data portal; in the VHA, partnerships and collaboration are prevalent	Opportunity	"	"
Collaboration across groups performing genome sequencing in healthy individuals will contribute to outcomes research; VHA MVP and NIH Precision Medicine Initiative collaboration to benefit all Americans; MVP is recruiting for the NIH Precision Medicine Initiative; partnering with academics and commercial organizations to bring value to patients; the VHA's CSP has experience and infrastructure to partner; VHA to partner with ClinGen; VHA to partner with pharma and other federal agencies to promote precision medicine	Opportunity	Collaboration within organization	"
Partnered research requires data sharing; share data to promote partnerships/ collaboration; Sharing data across health systems	Opportunity	"	"
Barrier to partnership; data-sharing option not in the informed consent; data sharing with partners in research; data sharing of clinical information between VHA and non-VHA care	Challenge	"	"
Apply HSR framework to transition from patient-level outcomes to population-level outcomes	Opportunity	Planning	Process

Table 1 continued

Paraphrased statements	Opportunity or challenge	Conference themes	CFIR constructs	CFIR domains
Logic model component: activities; concept: precision medicine practice Off-label use of drugs targeting tumor sequence variants Pharmacy benefits management as model to negotiate costs for precision medicine Lack of evidence for genotype-phenotype correlation; does precision medicine require a different level of proof compared with other medical acts or applications; lack of guidelines results in need for expert opinion Complexity of information coming from different laboratories can contribute to discordant information Precision medicine implementation involves many different partners and services Patient as advocate to raise awareness about genetic conditions Variation across VHA and biases contribute to inequities to access The need to use non-VHA care (e.g., limited obstetrics-gynecology genetics in VHA) Models for pre-emptive care to identify individuals at risk	Opportunity Opportunity Challenge Challenge Opportunity Challenge Opportunity Challenge Opportunity Challenge Opportunity	Improve access Care models Evidence-based practice Reduce variation Care coordination Improve access Reduce variation Care models Care models Improve access Care coordination Care models Improve access Reduce variation Reduce variation	Relative advantage Costs Evidence strength and quality Complexity Implementation climate Structural characteristics Available resources Access to knowledge and information " " " " Planning " " " " Executing	Intervention characteristics " " " " " " Inner setting " " " " " " Process " " " " " " Process
How do we identify at-risk individuals appropriate for referral to precision medicine? Data integration/return of genetic test results in the EHR Pharmacy benefits management model to deliver precision medicine; newborn screening as a model infrastructure; genomics integrated in other specialties Increase access to testing by reconciling institutional policies Variation in policies relating to precision medicine practice within VHA Variation in precision medicine care, or lack of precision medicine care; variation in evidence-based precision medicine practices; need to balance what is relevant to research and academically interesting with what is valuable for the care of individual patients	Challenge Opportunity Challenge Challenge Opportunity Challenge	Educate providers Educate providers Educate leadership Educate patients Educate providers Educate providers	Available resources Readiness for implementation Leadership engagement Knowledge and beliefs about the intervention Executing	Inner setting " " " " Individual characteristics " " Process
Logic model component: activities; concept: precision medicine education Educate the future workforce who will use precision medicine by connecting clinical, research, and academic/teaching activities Preparing the workforce for precision medicine Keeping decision-makers informed about what is actionable Poor genetics literacy among the public; barrier to implementation: educational needs of patients Barrier to implementation: educational needs of providers Variation in care due to variation in knowledge about precision medicine	Opportunity Challenge Challenge Challenge Opportunity Opportunity Opportunity Opportunity Opportunity Opportunity Challenge Challenge Challenge Opportunity Opportunity Challenge	Genetic diagnosis Medical management Beyond medical context Inform triggers Implications for family Eligibility for clinical trial Personal utility Clinical utility Clinical utility Personal utility Health-care utilization if "sick" Health-care utilization if "healthy" Health-care utilization if "healthy"	Relative advantage " " " " " " " " " " Evidence strength and quality Relative advantage Compatibility Relative advantage Relative advantage Self-efficacy	Intervention characteristics " " " " " " " " " " " " Intervention characteristics " " Individual characteristics Intervention characteristics " " Inner setting Outer setting Intervention characteristics
Logic model component: outcomes; concept: utility How to define personal utility. Is it clinical utility that has not been defined yet? Lack of evidence to support an effect of precision medicine on outcomes; identifying utility for genetic testing Context is critical for defining precision medicine outcomes; assessing utility that is not directly medical but may improve longer-term outcomes Patients help define outcomes and broaden definition of utility; engage patient to define personal utility and patient values, and to help inform coverage policies	Challenge Challenge Challenge Opportunity Opportunity Challenge	Personal utility Clinical utility Clinical utility Personal utility Health-care utilization if "sick" Health-care utilization if "healthy" Health-care utilization if "healthy"	Evidence strength and quality Relative advantage Compatibility Relative advantage Relative advantage Self-efficacy	Intervention characteristics " " " " Inner setting Intervention characteristics " " Individual characteristics Intervention characteristics " " Inner setting Outer setting Intervention characteristics
Logic model component: outcomes; concept: health-care utilization Ending diagnostic odyssey should decrease health-care utilization and costs Pre-emptive screening at the population level Participation in surveillance (for early disease detection) based on precision medicine information	Opportunity Opportunity Challenge	Define value of precision medicine Value for individual or population Coverage and reimbursement Define value of precision medicine Coverage and reimbursement	Evidence strength and quality Cost Compatibility External policy and incentives	Intervention characteristics " " " " Inner setting Outer setting Intervention characteristics
Logic model component: impacts; concept: precision medicine value Estimating the value of information brought by precision medicine, managing differences in perspectives between clinicians, patients, and policymakers Limited evidence on precision medicine value for populations; often not represented in clinical trials Cost of genetic testing is barrier Involve the veteran in defining value Barrier to coverage: clinicians and policymakers may not agree on when a test is most informative (i.e., discordance on eligibility criteria); understanding payer perspective on reimbursement; reimbursement for precision medicine; reimbursement is a barrier to adoption/implementation; reimbursement for reproductive services; policies/rules/laws that limit precision medicine practice	Challenge Challenge Challenge Opportunity Challenge	Diversity	Adaptability	Intervention characteristics
Logic model component: impacts; concept: equity and access Genomics can help to recognize variation in patient populations	Opportunity	Diversity	Adaptability	Intervention characteristics

Table 1 continued

Paraphrased statements	Opportunity or challenge	Conference themes	CFIR constructs	CFIR domains
Communicating uncertainty of genomic information; balance access to all information from precision medicine versus information that promotes patient empowerment and decision-making; informed consent is challenging, especially with the blurred line at the intersection of research and clinical practice; privacy issues and consequences of genomic information in the long term	Challenge	Communication	Complexity	"
Difficulty in reaching equipoise because of marked beliefs about precision medicine	Challenge	Ethical, legal, and social issues	Culture	Inner setting
Rare disease is not on anyone's radar	Challenge	Vulnerable population	Relative priority	"
Ethics of sharing genetic test results that are made in the research setting (e.g., ACMG recommended list of 59 genes)	Challenge	Ethical, legal, and social issues	Access to knowledge and information	"
Ethical issues pertaining to precision medicine	Challenge	Potential harms	Patient needs and resources	Outer setting
Need to assess access to testing and use of testing among vulnerable populations to identify barriers	Challenge	Vulnerable population	"	"
Precision medicine should reflect diversity of United States	Challenge	Diversity	"	"
Defining the threshold for ordering genetic tests and what will be covered; balance of personal utility and fair allocation of resources; a broad or narrow definition of medical necessity may have legal implications (i.e., services needed/required to receive a diagnosis or treatment); federal law (GINA) does not protect veterans; concerns about genetic discrimination	Challenge	Ethical, legal, and social issues	External policy and incentives	"
Risk of knowing about precision medicine diagnosis	Challenge	Potential harms	"	"
Fear of genetic diagnosis	Challenge	Potential harms	Knowledge and beliefs about the intervention	Individual characteristics
Logic model component: impacts; concept: economic indicators				
Return on investment for early cancer detection and prevention	Opportunity	Return on investment	Relative advantage	Intervention characteristics
Increased health-care utilization resulting from sequencing of healthy individuals; value of testing in healthy people; gain in information versus increased health-care utilization	Challenge	Return on investment	Cost	"
Decision support tools to identify the most cost-effective testing strategy	Opportunity	Cost-effectiveness	"	"
Defining value for cost-effectiveness analyses; include costs relating to personal burden for patient in economic analyses	Challenge	"	"	"
<i>ACMG</i> American College of Medical Genetics and Genomics, <i>CFR</i> comparative effectiveness research, <i>CFR</i> Consolidated Framework for Implementation Research, <i>CSP</i> Cooperative Studies Program, <i>CLIA</i> Clinical Laboratory Improvement Amendments, <i>EHR</i> electronic health records, <i>GINA</i> Genetic Information Non-discrimination Act, <i>HSR</i> health services research, <i>MVP</i> Million Veteran Program, <i>NIH</i> National Institutes of Health, <i>RAND</i> Research and Development Corporation, <i>VHA</i> Veterans Health Administration, <i>VIREC</i> Veterans Affairs Information Resource Center.				
CFIR constructs not included, by domain: intervention characteristics: intervention source, trialability; outer setting: peer pressure; inner setting: tension for change, organizational incentives and rewards, goals and feedback, learning climate; individual characteristics: individual stage for change, individual identification with organization, other personal attributes; process: engaging opinion leaders, formally appointed internal implementation leaders, champions, external change agents.				

Table 2 Conference themes stated as strategies and mapped to the ERIC compilation of implementation strategies and logic model

Paraphrased statements	Conference themes	ERIC implementation strategies	ERIC clusters
Logic model component: inputs; concept: infrastructure			
Modify existing databases to integrate new types of data (e.g., record somatic variants in ClinVar)	Information technology and clinical informatics infrastructure	Use data warehousing techniques	Adapt and tailor to context
Embedding genetics/genomics into bulk of EHR data; develop a research-ready EHR to integrate data from multiple sources	Information technology and clinical informatics infrastructure	Change record systems	Change infrastructure
Computing environment needed for data sharing and collaboration; build information technology and clinical informatics infrastructure to support bio-banking efforts (e.g., VHA MVP); create a platform open to any phenotypes for precision medicine research; develop an interface (e.g., mobile apps) to deliver genetic test reports to the EHR/data warehouse; to keep data fresh and expand resources, provide an infrastructure that integrates/updates data rapidly, and provide analysis tool for researchers to use the data remotely	Information technology and clinical informatics infrastructure	Change physical structure and equipment	"
To educate providers and promote research: VHA research education and clinical centers of excellence (e.g., MIRECC); disseminate best practices via Centers of Excellence to reduce variation; create a precision medicine research network across the VHA	Information technology and clinical informatics infrastructure	Start a dissemination organization	"
Logic model component: inputs; concept: big data			
Integrate quality metrics within the EHR to maximize information and build a learning system	Data analytics	Develop and implement tools for quality monitoring	Use iterative and evaluative strategies
Real-time monitoring to evaluate use of precision medicine and changes in care	Data analytics	Develop and organize quality monitoring systems	"
Use publically available databases (ClinVar) to help with interpretation of genetic data/genotype-phenotype; worldwide partnerships to understand genotype-phenotype correlations	Data analytics	Use data experts	Adapt and tailor to context
Data warehousing techniques to monitor outcomes/dashboard; data integration at the patient and population level to guide care	Data analytics	Use data warehousing techniques	"
Use of database/registry to benchmark/standardize care	Data sources	"	"
Data mining to inform test interpretation (e.g., IBM Watson); informatics core (data warehouse) and data broker to de-identify data for research	Data mining	"	"
Official registries to standardize annotations	Data standards	"	"
Integrate information across specialties; integrate information from clinical research and patient care; partner with clinical reference laboratories to obtain genetic/genomic test results not readily available in the electronic health record	Data sources	Capture and share local knowledge	Develop stakeholder inter-relationships
Integrate decision support tools in the EHR; support providers in treatment decisions: integrate decision support in existing EHR systems; integrate within laboratory results and pharmacy sections; support to integrate data from different tests/technology/departments and provide a comprehensive report to providers with action plan; return of results that includes educative material for providers and patients, designed with their input; obtain discrete data from genetic testing to improve documentation and	Data analytics	Facilitate relay of clinical data to providers	Support clinicians

Table 2 continued

Paraphrased statements	Conference themes	ERIC implementation strategies	ERIC clusters
communication in the medical record, including the personal health record; use electronic tools to increase guideline-directed ordering and reduce variations/disparities			
Use of online action plan for patients to track, monitor, and remind them of their participation in surveillance for early disease detection	Data analytics	Intervene with patients/ consumers to enhance uptake and adherence	Engage consumers
Maximize the information: integrate genetic test results with family linkage; annotation of genetic test results in the EHR; use published guidelines/guidance for annotation and do not allow clinicians to provide input	Data analytics	Change record systems	Change infrastructure
Promote interoperability and portability to help information exchange between clinics	Data standards	"	"
Logic model component: inputs; concept: resources			
Champions for precision medicine in information technology and clinical informatics to meet information technology and clinical informatics challenges	Workforce	Identify and prepare champions	Develop stakeholder inter-relationships
Expand clinical genetic services through hiring of clinical geneticists	Workforce	Build a coalition	"
Pay for clinical testing to determine eligibility for clinical trials	Funding	Fund and contract for the clinical innovation	Utilize financial strategies
Conferences funding (e.g., National Academy of Sciences roundtable); action collaborative to identify outcomes that are meaningful to measure the impact of precision medicine on the delivery of care	Funding	Start a dissemination organization	Change infrastructure
Logic model component: activities; concept: precision medicine research			
Understand the contextual factors that influence the use of precision medicine in practice to improve processes and outcomes	Health services research	Assess for readiness and identify barriers and facilitators	Use iterative and evaluative strategies
Health services research can bridge the gap between research and clinical practice; health services research can thread the needle at the intersection of research and practice	Health services research	Stage implementation scale-up	"
Data sharing to inform outcomes for n-of-1 clinical trials; data sharing for n-of-1 case; collaborations/ data sharing to facilitate precision medicine research	Data sharing	Capture and share local knowledge	Develop stakeholder inter-relationships
Partnership between academic institution and private sector; partnership outside VHA to get access to expertise; partner with other organizations to facilitate precision medicine research	Collaboration across sectors	Develop academic partnerships	"
Intramural programs to foster partnerships within the VHA	Collaboration within an organization	"	"
Convene stakeholders and create a research network; publish findings	Collaboration across sectors	Promote network weaving	"
Reaching out to the community to inform precision medicine research; patients to inform precision medicine research agenda; engage veterans to guide policy on data sharing of biobank data (e.g., VHA MVP data)	Engage public	Involve patients/consumers and family members	Engage consumers
Build trust with consumers/patients to encourage data sharing; public access to aggregated data from precision medicine research; return of aggregate findings from precision medicine research	Data sharing	Prepare patients/consumers to be active participants	"
Economic incentives to share data/collaborate	Data sharing	Alter incentive/allowance structures	Use financial strategies
Partnership and genetic test cost sharing with industry partners	Collaboration across sectors	Use other payment schemes	"

Table 2 continued

Paraphrased statements	Conference themes	ERIC implementation strategies	ERIC clusters
Logic model component: activities; concept: precision medicine practice Management of testing resources and oversight of utilization	Reduce variation	Facilitation	Provide interactive assistance
Use gatekeepers following guidelines to ensure appropriate testing; genetic testing services restricted to genetics provider acting as a gatekeeper (in response to challenge of disparities linked to coverage/access to precision medicine); genetics professional acts as gatekeeper for genetic testing services; payers require pre-authorization for genetic testing; must provide clinical reason for testing	Reduce variation	Provide clinical supervision	"
Regional guidelines for genetic counseling and testing referral expertise; centralized genetic services (genetic consultation and genetic counseling); centralized genetics expertise through use of telehealth; centralize expertise for precision medicine education and dissemination	Reduce variation	Centralize technical assistance	"
Centralized technical assistance to address the barrier of limited clinical genetics	Improve access	"	"
Leverage existing capabilities; off-label use of drugs	Improve access	Promote adaptability	Adapt and tailor to context
VHA is big and can leverage its size/economies of scale to disseminate best practices to ensure access of precision medicine to veterans	Improve access	Use data experts	"
Precision medicine care should be driven by clinical scenario/context rather than availability of a specific genetic test; to optimize precision medicine use and coverage, develop precision medicine practice based on the informational needs for clinical decision, not a genetic test	Improve access	Tailor strategies	"
Leadership is a key factor promoting the successful implementation of genomic medicine	Improve access	Recruit, designate, and train for leadership	Develop stakeholder inter-relationships
Change the culture of the genetics community to eliminate genetic exceptionalism largely based on costs that will become irrelevant; little equipoise between those who use precision medicine and those who require a robust evidence base for its use; should have neutral stance on value of genomics as opposed to beating up on our biases	Improve access	Conduct local consensus discussions	"
Dissemination of best practices through inter-regional work groups	Reduce variation	Use advisory boards and work groups	"
Communications and stakeholder engagement are factors that promote the successful implementation of precision medicine; partnership with leadership and patients is key to promoting precision medicine practice across VHA specialties; network and programs to build partnerships, collect and standardize knowledge, and disseminate what works across institutions; regional genetics collaborative, a model for precision medicine implementation that involves collaboration with multiple stakeholders; partnerships to provide off-label drugs	Improve access	Promote network weaving	"
Care models that bundle precision medicine services (e.g., consultation and genetic testing)	Care models	Revise professional roles	Support clinicians
Use of genetic counselors to facilitate integration of genetics within practice of non-geneticist (i.e., emerging model of genetic health care)	Care models	Create new clinical teams	"
To manage precision medicine coverage: apply principles of off-label drug use to precision medicine in formulary management—accept a lower level of evidence for precision medicine if it is deemed beneficial	Improve access	Place innovation on fee for service lists/formularies	Utilize financial strategies

Table 2 continued

Paraphrased statements	Conference themes	ERIC implementation strategies	ERIC clusters
Use policy as a starter for precision medicine use, until it can be driven by evidence; limit top-down policies given the variability across the VHA system	Improve access	Mandate change	Change infrastructure
Need to develop policy for all levels of clinical expertise across the health-care system; policies that require data integration and discrete data collection to reduce variation in precision medicine practice	Reduce variation	"	"
Change information technology and clinical informatics systems to promote the successful implementation of precision medicine	Improve access	Change record systems	"
Integrate annotation tools within the EHR to improve reproducibility	Reduce variation	"	"
Tele-genetics; video-teleconferencing to improve access to precision medicine; telehealth to enable access to genetics professionals; leverage the centralized nature of the VHA to deploy tele-genetics; telehealth for genetic counseling to remedy local lack of genetics expertise	Improve access	Change physical structure and equipment	"
Patients referred to research program for diagnosis; genetic diagnosis made by research projects; embed precision medicine research in clinical care; centralize processes and embed research in the clinic to increase access to clinical trials; incorporate precision medicine into the VHA's national Pharmacy Benefits Management program to decrease variations in access to precision medicine; to educate providers about precision medicine, support research, education, and clinical care done together	Care models	Change service sites	"
Centralized services for individuals with genetic disease	Reduce variation	"	"
Logic model component: activities; concept: precision medicine education			
Telehealth, SCAN-ECHO (provider -to-provider telehealth encounter) to support uptake of precision medicine clinical pathways by providers	Educate providers	Provide ongoing consultation	Train and educate stakeholders
Educate policymakers about precision medicine	Educate leadership	Conduct educational meetings	"
Centralized program for precision medicine education for providers	Educate providers	Create a learning collaborative	"
To minimize variations in precision medicine, establish policies and protocols to educate providers	Educate providers	Mandate change	Change infrastructure
To educate providers and promote research, develop research, education, and clinical centers (e.g., the VHA's MIRECC)	Educate providers	Change service sites	"
Logic model component: outputs; concept: precision medicine diagnosis			
Precision medicine research enterprise solely, protocol does not allow return of results to participants	Precision medicine diagnosis	Mandate change	Change infrastructure
Logic model component: outcomes; concept: utility			
Use comparative effectiveness research to contribute to evidence base	Clinical utility	Purposefully re-examine the implementation	Use iterative and evaluative strategies
Technology assessment to help measure clinical utility	Clinical utility	Use data experts	Adapt and tailor to context

Table 2 continued

Paraphrased statements	Conference themes	ERIC implementation strategies	ERIC clusters
Logic model component: impacts; concept: precision medicine value			
De-implementation of technology that has no added value	Value for individual/population	Purposefully re-examine the implementation	Use iterative and evaluative strategies
Review committee for utilization of tests that are not in the EHR system (i.e., previous authorization)	Coverage and reimbursement	Provide local technical assistance	Provide interactive assistance
Base coverage on evidence level/value; change in reimbursement; compensation based on workload (i.e., RVUs); provider stewardship of precision medicine applications	Coverage and reimbursement	Alter incentive/allowance structures	Utilize financial strategies
Logic model component: impacts; concept: equity and access			
Monitor outcomes to understand disparities in precision medicine	Potential harms	Develop and organize quality monitoring systems	Use iterative and evaluative strategies
Promote health equity by preplanning and considering the possibility of disparities	Potential harms	Develop a formal implementation blueprint	"
Advocate from within to promote equity and access to precision medicine; leadership to promote equity and access to precision medicine	Communication	Inform local opinion leaders	Develop stakeholder inter-relationships
Include patient perspective in technology assessment of precision medicine applications; patient advisor to integrate the patient perspective in precision medicine practice	Communication	Involve patients/consumers and family members	Engage consumers
Data privacy committee chaired by a patient to ensure privacy and patient trust while increasing data sharing; evaluation of what patients may want to ensure equitable access to (genetic) testing and counseling	Ethical, legal, and social issues	Communication	"
Oversample minorities to overcome disparities in precision medicine research	Ethical, legal, and social issues	Intervene with patients/ consumers to enhance uptake and adherence	"
Cultural sensitivity in recruitment and informed consent	Diversity	"	"
Partnerships and policies that ensure cultural aspects are addressed to ensure equity	Diversity	Mandate change	Change infrastructure
Executive order protects veterans from genetic discrimination	Ethical, legal, and social issues	"	"
Logic model component: impacts; concept: economic indicators			
Use economic analysis and modeling to analyze value of precision medicine	Cost-effectiveness	Model and simulate change	Develop stakeholder inter-relationships

Strategies not identified, by ERIC cluster: use evaluative and iterative strategies; audit and provide feedback, conduct local need assessment, conduct cyclical small tests of change, and obtain and use patients/consumers and family feedback; develop stakeholder inter-relationships: organize clinician implementation team meetings, obtain formal commitments, identify early adopters, use an implementation advisor, visit other sites, involve executive boards, and develop an implementation glossary; train and educate stakeholders: conduct ongoing training, develop educational materials, make training dynamic, distribute educational materials, use train-the-trainer strategies, shadow other experts, work with educational institutions, and conduct educational outreach visits; support clinicians and develop resource-sharing agreements; engage consumers: increase demand and use mass media; utilize financial strategies: access new funding, make billing easier, alter patient/consumer fees, develop disincentives, and use capitated payments; change consumers: change credentialing and/or licensure standards, change accreditation or membership requirements, and change liability laws.

EHR electronic health record, ERIC Expert Recommendations for Implementing Change, MIRECC Mental Illness Research, Education and Clinical Centers of Excellence, MVP Million Veteran Program, NA not applicable, RVU relative value unit, VHA Veterans Health Administration.

integrated health-care systems and information technology and clinical informatics are inputs that provide opportunity for precision medicine implementation, precision medicine practice faces fundamental challenges that must be overcome to realize the promise of precision medicine. These challenges include an unprepared health-care workforce, the need for evidence-based clinical guidance, and the need for novel care models that address the diversity of the US population, and provide equitable access, improve care coordination, and reduce variation in precision medicine practice. Additionally, while there is considerable enthusiasm about the promise of precision medicine outputs (e.g., diagnosis, risk assessment, and targeted treatment) and cautious optimism about outcomes from precision medicine interventions (i.e., clinical utility, personal utility, and targeted health-care utilization), the longer-term impacts of precision medicine are fraught with challenges relating to uncertainties about the value of precision medicine, equity of and access to precision medicine, cost-effectiveness, and return on investment.

We used the CFIR to systematically assess potential barriers and facilitators to precision medicine implementation, which can facilitate collaborations and evaluation across organizations.¹² The Implementing GeNomics In PracTice (IGNITE) Network's Common Measures Working Group also used the CFIR to develop standardized measures to inform implementation research.¹⁶ However, the IGNITE work group found that the CFIR did not capture factors relevant to community values for patients and families, such as "understanding patient perceptions, anxiety, and personal utility." We also identified themes relevant to patient experience and personal utility. However, our perspective was that of a health-care organization and we viewed patients as stakeholders within the health-care organization. As such, we mapped patient experience within the CFIR domain, "characteristics of individuals", and personal utility within the CFIR constructs of "evidence strength and quality", and "relative advantage" within the domain, "intervention characteristics".

We identified 42 discrete implementation strategies from the ERIC compilation that leverage the opportunities and address the challenges for precision medicine implementation. All conference themes representing a strategy were depicted within the ERIC compilation of implementation strategies. However, the saliency of the strategies described for precision medicine implementation may differ from other innovations. As described by Waltz and colleagues, a panel of implementation science and clinical experts rated the importance and feasibility of all implementation strategies included in the ERIC compilation.¹⁵ The goal was to help facilitate the selection of strategies that are best suited for implementation efforts. These experts gave low ratings for both importance and feasibility to the strategies within the cluster of "change infrastructure" (e.g., change record systems, change physical structure and equipment, and change service sites). These strategies frequently came up as key during the discussions regarding precision medicine implementation. Conference participants identified information technology

and clinical informatics infrastructure changes and integration of data analytics as critical to successful precision medicine research, effective precision medicine practice, and facilitating a learning health-care system. They identified changes in service sites, such as embedding precision medicine research within clinical precision medicine practice, as necessary to promote new care models that could increase access to and decrease variation in precision medicine practice. Thus, while these strategies may have low feasibility, they appear to have high importance to successful precision medicine implementation.

Many of the precision medicine implementation strategies we identified in the analysis of the conference proceedings have been described by others.^{2,5-8} However, the contribution of diverse stakeholders facilitated the development of a wide range of precision medicine implementation strategies, some of which have not been reported previously, such as using centralized technical assistance for genetic consultation through the use of telehealth to reduce variation in precision medicine practice, and using formularies for genetic tests to improve access to precision medicine by facilitating coverage and reimbursement. Moreover, to our knowledge, this is the first attempt to characterize a comprehensive list of precision medicine implementation strategies according to the ERIC compilation to facilitate precision medicine program planning and evaluation.

The IGNITE network has published work describing seven ERIC implementation strategies addressing challenges that are common to the six implementation projects within their network, most of which we describe (i.e., use data warehousing techniques, conduct educational meetings, prepare patients to be active participants, and involve patients) and some we have not (i.e., develop educational materials, conduct educational outreach in clinical settings, and use mass media to engage patients).⁸ While these implementation strategies utilized by IGNITE were not explicitly mentioned by the conference participants, several other strategies regarding provider education and patient engagement were mentioned. Thus, our wide-ranging list of implementation strategies that includes strategies from all clusters within the ERIC compilation is not exhaustive, but is satisfactory for contextualizing the logic model components and concepts that can be used for precision medicine program planning and evaluation.

Research topics mentioned during the conference provide the basis for a research agenda that could fill the evidence gaps for precision medicine. The research areas we identified span the continuum of translation research for genomic medicine, as described by Khoury *et al*.¹⁷ Yet, the need for health services, outcomes, and dissemination and implementation research dominated the conference discussions, consistent with the conference goal, and in keeping with previous work showing limited funded research and publications in these areas.¹⁸

We learned that preclinical studies are still needed to define genotype-phenotype associations. For success, data sharing is

critical and could be achieved with partnered research through collaborations within health-care organizations and across sectors, and through public engagement to promote interest in precision medicine. Health services and outcomes research are needed to generate robust evidence for personal and clinical utility resulting from precision medicine interventions, and to better understand the contextual factors that influence the usefulness of precision medicine interventions. Dissemination and implementation, organizational, and provider behavior research are needed to help improve access to precision medicine and reduce variation in precision medicine practice. It will be essential to develop data standards and address the data extraction needs necessary for a learning health-care system.¹⁹ Research is also needed to determine how best to communicate the complexities of precision medicine information and to educate the workforce and public. Lastly, health services and economics research are needed to understand precision medicine care coordination and optimal models for the delivery of precision medicine interventions, barriers to coverage and reimbursement, and cost-effectiveness of precision medicine.

Important limitations to this work need mentioning. We used a structured process with instructions to the conference speakers that constrained their presentations, and while we engaged numerous individuals from a variety of stakeholder groups who contributed to the discussion, other viewpoints may not be represented. We used a predefined set of research topics to assist in thematic coding and we used coders who are knowledgeable about precision medicine research and practice, which may have influenced the thematic analysis. However, themes were derived from the data using dual independent coding to mitigate biases, and we have provided coded paraphrased statements in the tables to ensure transparency.²⁰

Conclusion

We have developed a logic model for precision medicine implementation within a health-care organization informed by key stakeholders that provides a roadmap for precision medicine program planning. Furthermore, we have contextualized the logic model through the use of implementation science frameworks. The domains and constructs from these frameworks provide a basis for prioritizing implementation strategies that can leverage facilitators and address barriers to enhance the adoption of precision medicine within a health-care organization. This formalized approach helps to organize and standardize precision medicine implementation and evaluation. Integrated health-care systems offer opportunities to realize the promise of precision medicine through the use of population-based data that can generate evidence regarding precision medicine outcomes and inform clinical decisions at the point of care. Preparing the health-care workforce and educating the public remain paramount to achieving successful precision medicine implementation. Implementation planning should consider novel care models, modes of delivery, and financial strategies to ensure access and reduce

variability to precision medicine interventions. Precision medicine programs should reflect the diversity of the populations served and incorporate stakeholder perspectives on the value of precision medicine interventions when evaluating the effectiveness of precision medicine implementation.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (<https://doi.org/10.1038/s41436-018-0315-y>) contains supplementary material, which is available to authorized users.

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DISCLOSURE

The authors declare no conflicts of interest.

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