Review Article
Leveraging implementation science to improve implementation outcomes in precision medicine

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Abstract: Background and Purpose: Introduction of omics technologies in clinical practice means increased use of validated biomarkers, through precision medicine (PM). Although implementation science (IS) affords an array of theoretical approaches that can potentially explain PM intervention uptake, their relevance and applicability in PM implementation has not been empirically tested. This article identifies and examines existing implementation frameworks for their applicability in PM, demonstrating how different IS theories can be used to generate testable implementation hypotheses in PM. Methods: A three-step methodology was employed to search and select implementation models: a scoping search in Google Scholar produced 15 commonly used models in healthcare; a systematic search in PUBMED and Web of Science using the names of each model as keywords in search strings produced 290 publications for screening and abstraction; finally, a citation frequency search in the 3 databases produced most cited models that were included in the narrative synthesis. Results: Main concepts and constructs associated with each of the 15 models were identified. Four most cited frameworks in healthcare were: REAIM, CFIR, PRISM and PARiHS. Corresponding constructs were mapped and examined for potential congruence to PM. A generalized PM implementation conceptual framework was developed showing how omics biomarker uptake relates to their evidence base, patient and provider engagement and Big data capabilities of involved organizations. Conclusion: We demonstrated how implementation complexities in PM can be addressed by explicit use of implementation theories. The work here may provide a reference for further research of empirically testing and refining the identified implementation constructs.

Keywords: Implementation science, precision medicine, genomic medicine, omics technologies, biomarkers

Introduction

Unparalleled biomedical discoveries related to precision medicine (PM) are shifting long held paradigms in healthcare. For instance, deeper insights into gene-environment-lifestyle interactions challenge the long held DNA-destiny belief by presenting evidence of environmental influence on inheritable traits; something once considered a genetic impossibility [1]. PM is an approach to disease that incorporates new molecular-level biomarkers, such as single nucleic polymorphism (SNP) in addition to the more familiar empirical and clinical symptom-based evidence. Improved insights into disease etiology due to these new biomarkers have ushered in a new era of diagnostic and therapeutic accuracy at both individual and population health levels [2, 3]. Omics technologies such as deep sequencing, mass spectrometry and microarrays, form the foundation of PM [4]. The exponential rate at which biomedical researchers discover novel biomarkers does not match the linear rate at which they are incorporated into routine clinical practice. This could be attributed to a host of ‘real-life’ challenges that meet biomarkers as they move beyond strictly-controlled ‘bench-side’ research settings. Such practicalities make the transfer of prospective biomedical findings into actual clinical practice and population health settings a contextually unique undertaking. Often, this can lead to expensive trial-and-error implementation expeditions, with no a priori reason to expect success, nor confidence in replicating success, if or when achieved [5]. Different implementation settings for the biomarkers...
may demand different implementation strategies. For instance, African settings differ from Asian and European settings on biological, social-cultural and economic scales [6]. Moreover, PM implementation straddles multi-disciplinary and complex landscapes which may demand better interdisciplinary collaboration, including across fields of medicine, science, public policy, law and ethics. In some cases, mismatch between strategies meant to address either hindrances or facilitators of PM implementation may significantly affect implementation outcomes [7]. Another PM implementation challenge is related to the evidence base of most PM interventions. For instance, evidence based on omics technologies presents daunting implementation challenges as it is often perceived a moving target whose reliability keeps on changing with newer discoveries. Furthermore, most PM interventions are likely not to follow the traditional basic science discovery-efficacy-effectiveness implementation model. This model assumes linearity in execution of scientific discoveries [8]. This may have considerable implications on the ability to evaluate the clinical utility of the biomarkers efficiently and at low-cost [9]. It is for these reasons that there is a general consensus in existing implementation literature that implementation efforts should be grounded in theory for optimal outcomes [10]. Implementation theories provide an opportunity for robust, testable and reproducible means of enhancing PM implementation success. They specify relations among implementation variables, thereby enabling prediction of implementation outcomes [11].

Even though the application of IS tools are generally in their infancy, these tools can be leveraged to bolster implementation efforts within the field of PM [12]. It has been noted that the once regarded “training-and-information-dissemination” process of bridging research-to-practice gap is no longer effective in producing measurable changes in practice [13]. In this systematic review, we propose a more systematic and precise use of IS theories and models in PM to effectively integrate and eventually routinize omics use of biomarkers in clinical practice. We demonstrate how different implementation theories can be used to generate testable hypotheses regarding factors that influence PM implementation. Lastly, we identify knowledge gaps and suggest areas that need further research to facilitate the real-world application of IS implementation models in PM.

**Implementation science and clinical application of omics technologies**

Advances in omics technologies such as next generation sequencing (NGS) make it possible to examine, in single experimentations, various biological processes or physiologic functions and structures about an individual’s genetic make-up. The large amounts of biological data are represented most prominently by genomics, proteomics and metabolomics including collections of molecules such as amino acids, sugars and fats in a given tissue. Availability of omics technologies and the desire to replace known traditional but suboptimal diagnostics with improved biomarkers underlies a renewed drive towards a more predictive, preventive and stratified medicine [14]. Validated OBMs have been used to measure biological alterations or fluctuations and make prediction, diagnosis, progression, or outcome of a treatment or disease more precise. OBMs have important biomedical, clinical and economic implications. Use of OBMs in patient stratification with respect to the use of trastuzumab and imatinib drugs [15] is an excellent example. Moreover, surrogate end point OBMs (those that yield information on the clinical benefit/survival at earlier stages indicative of clinical endpoints in drug development) are clinically useful, especially for expedited regulatory or therapeutic decisions regarding candidate drugs. This not only helps to bring new medicines to the right patients faster, but also reduces cost for developing novel therapeutic targets through early proof-of-concept [16]. Potential benefits of OBMs range from expedited clinical trials, reduced novel therapeutic development costs, targeted therapies and drug dosages to use in patient stratification. However, despite these demonstrated benefits there is a general lack of a coherent workflow connecting OBMs to suitable clinical end point through appropriate implementation strategies. Generally, implementation of OBMs sits at the terminal point of a traditional research-utility knowledge translation continuum.

**Figure 1** illustrates an OBM discovery pipeline juxtaposed along traditional pharmacological drug discovery process. Information gleaned
from bio-samples at the beginning of the OBM development pipeline can indicate the state of health or disease on a patient, including information about gene mutations (genomics), microRNA expression profiling (transcriptomics and proteomics) and metabolites (metabolomics). OBMs’ validity and fit-for-purpose status, robustness, reproducibility, and feasibility are critical to their clinical validity, and must be considered.

Clinical application of OBMs include disease screening, diagnosis rule-in or rule-out, prognosis assessment, intervention eligibility assessment, intervention or treatment (dosage) adjustment, intervention efficacy assessment and to assess compliance for regulation purposes. Generally, there are two types of OBMs: disease-related OBMs which give an indication of the probable effect of an exposure on patient (risk indicator, or predictive OBMs [17]), whether a disease already exists (diagnostic OBM), or how such a disease may develop in an individual case regardless of the type of treatment (prognostic OBM) [18]. In contrast, drug-related OBMs indicate whether a drug will be effective and/or safe in a specific patient and how the patient’s body will process it.

Whereas translational research is about basic science discoveries and early-stage implementation of interventions within clinical and public health settings (Figure 1), implementation research, on the other hand, aims to ensure validated discoveries are turned into improved health outcomes for entire communities. Healthcare is normally provided under dynamic and resource-constrained settings which demand evidence-based, theoretical and pragmatic strategies to ensure effective integration of new research findings into clinical care [19]. This implies a rigorous interrogation of implementation factors that may cause clinical application of new discoveries to either fail or succeed, while optimizing resource utility [20]. However, paucity of theoretical underpinnings for implementation efforts particularly in PM casts expected results into uncertainty, with little prospect of explaining how and why the outcomes were a success or failure [21], thus obliterating chances of pinpointing criteria for future implementation success. The solution however, lies in a theoretical framework that provides better understanding and explanation of how and why implementation succeeds or fails [21]. Implementation science plays the
critical role of providing such theoretical and pragmatic tools to support implementation efforts.

A constantly changing evidentiary base of omics technologies implies most PM implementation initiatives may be rendered ‘once-off’ efforts, frequently non-interoperable across different clinical settings. Implementations without a well-defined theoretical basis therefore, offers little insight and guidance on implementation across contexts and settings. This may lead to ad hoc assortment of unstandardized PM implementation initiatives that are neither generalizable, reproducible, nor sustainable [12]. So far, there is little research that has consolidated disparate theories and models to inform implementation of PM at health systems level. In the next sections, we describe how PM implementation may benefit from appropriate IS theories and models, and how this may allow for tailoring of implementation plans that are adaptable to different contexts.

Methods

In this review, precision medicine (PM) refers to settings at either or both biomedical research and clinical practice. At biomedical research settings, PM constitutes the discovery and validation of omics-based biomarkers, mainly using omics technologies (tools used to measure global molecular constituents-e.g. genomics, proteomics, metabolomics). At clinical practice settings, it refers to the use of omics-based biomarkers for personalized or stratified treatment regimens. In this study, a theory refers to a less practical but conceptual arrangement of ideas or statements held as an explanation or account of a group of facts or phenomena [22], while a model means a more practical, simplified representation of reality [23].

The methodology used in this paper is summarized in Table 1.

Search strategy and selection of publications

Based on available literature we identified commonly used frameworks. We did this by conducting a general search for the commonly used implementation models using the key words, “implementation theories, models and frameworks in healthcare” in PUBMED. We selected PubMed because it represents the pre-eminent database of peer-reviewed literature in health-related fields, because we wanted to confine our search to implementation models specific to healthcare, rather than generic implementation. We then identified common implementation frameworks using names used to refer to the models; Table 1 shows the summary of methodological process while Figure 2 presents literature search and selection process. To get the most cited implementation frameworks, we searched for models that had been identified in the first stage in 3 databases: PubMed, Web of Science and Google Scholar. The cumulative citation frequencies for each model were then summed up and presented graphically (Figure 3).

Inclusion and exclusion criteria

The a priori inclusion criteria for the papers were: published peer-reviewed literature, English language, published between 2009 and July 2019, and explicit or extensive focus on healthcare. Exclusion criteria: sole focus on High income countries (HICs); narrow focus on implementation models for specific diseases (e.g. oncology).

Appraisal

The inclusion/exclusion criteria were used to identify commonly used models in the field. We did not evaluate the overall effectiveness of these models; rather, we used these common models to highlight diversity of theoretical underpinnings and that precision medicine implementation efforts can be anchored on the models’ separate strengths.

Abstraction of articles

Abstraction involved finding out what constructs were stated in the papers as being associated with the identified models and a considered judgement on analysis levels ascribable to each of the models. Drafts were distributed and reviewed by all coauthors and refinement comments incorporated.

Results and discussion

Figure 2 presents the results of the systematic literature search and selection process based on the Preferred Reporting Items for Systematic
Table 1. Summary of methodology

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<thead>
<tr>
<th>Step</th>
<th>Activity</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Identification of most common implementation frameworks in existing literature</td>
<td>A literature search using “Implementation theories, models and frameworks in healthcare” in PUBMED.</td>
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<td>2</td>
<td>Systematic search of publications related to the identified implementation models in PUBMED and Web of Science databases over a ten-year period</td>
<td>(a) definition of keywords - names of the frameworks in quotes (““) and healthcare (e.g. “Consolidated Framework for Implementation of research”).</td>
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<td>(b) use of the Boolean “AND” operator.</td>
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<td>(c) limits: publication period: 2009-July 2019 (10 years); languages: English; Titles (TI).</td>
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<td>(d) manual search performed by snowballing using references in admitted papers; and by recommendation.</td>
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<td>3</td>
<td>Citation frequency search for representative publications of the models (e.g. citation for original publication of each model) in 3 databases (PUBMED, Web of Science and Google Scholar)</td>
<td>Finding and summing up citation frequencies in the 3 databases for each model to find their order of cumulative citations (Figure 3).</td>
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<tr>
<td>4</td>
<td>Narrative synthesis</td>
<td>Findings were used to relate the implementation models to precision medicine.</td>
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Reviews and Meta-analyses (PRISMA) guidelines [24]. The review made derivations of theoretical frameworks relevant to implementation of precision medicine. In total, fifteen frameworks were identified and are further detailed in the following section.

Theories, models and frameworks applicable to implementation of precision medicine

The identified frameworks, theories and models generally differ in their focus, perspective and underlying paradigms as they are drawn from various disciplines. The disciplines include medicine, public health, psychology, organizational studies, political science, and agriculture. Table 2 presents the results of literature abstraction. Although the frameworks refer to implementation tools generally applicable to the field of healthcare, some elements specific to each may particularly be fundamental in laying the foundation for suitable PM implementation models. Table 2 further indicates implementation constructs corresponding to the stated frameworks and their levels of analysis.

Levels of analysis give a better understanding of the multi-level complexity involved in implementing precision medicine. Factors that could influence implementation process may be premised at different or multiple analysis levels, including at innovation, individual, organizational, or systems level.

Figure 3 presents the results of a search for commonly cited implementation frameworks in existing literature and ranked according to their citation frequencies. The theories searched for are stated under “Key”. The data were obtained from PubMed, Web of Science and Google Scholar databases within the past ten years (January 2009-July 2019).

From Figure 3, the first four most cited implementation frameworks were: Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM), Promoting Action on Research Implementation in Health Services (PARIHS), Practical, Robust Implementation and Sustainability Model (PRISM) and Consolidated Framework for Implementation Research (CFIR).

The RE-AIM framework

The RE-AIM Framework has been termed an evaluation framework [25]. It conceptualizes implementation outcomes of an intervention as a function of five factors: Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM). The model has both implementation and dissemination considerations on equal footing as it was initially aimed at improving reporting on key issues related to implementation and external validity of health-related literature. RE-AIM addresses concerns of using research conducted under optimal efficacy condi-
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The former is the case in most translational studies and is often the “gold standard” for decision-making and guidelines. RE-AIM elements follow a logical sequence, beginning with adoption and reach, followed by implementation and efficacy or effectiveness, and ending with maintenance. It focuses on the “Reach” of an intervention—is the intervention getting to the target population, an individual-level measure of participation that refers to the percentage and risk characteristics of persons who receive or are affected by an intervention or policy program; “Effectiveness”-is the intervention effective in the real world setting; “Adoption”-are target groups adopting the intervention, referring to the proportion and representativeness of settings that adopt the intervention; “Implementation”-what is the fidelity, i.e., the degree to which the intervention is implemented as originally intended; and “Maintenance” or sustainability-are the effects of the intervention maintained over time, measuring the extent to which innovations become a relatively stable, enduring part of the behavioral repertoire of an individual, organization or community [26]. RE-AIM fits with systems-based approaches and the social-ecological model and is most useful for providing an evaluation of interventions that address multiple causes and holistic systems [27]. Each RE-AIM dimension provides a different measurable outcome for evaluating effectiveness. Using these measures, RE-AIM can be used to break down, evaluate, and even plan PM programs by helping identify pragmatic priorities. This focus on real world pragmatic questions enables the utilization of already available data and outcomes and presents an opportunity for intervention within each dimension of the framework. Using REAIM, the impact (I) of an intervention is the product of the reach (R) and the efficacy (E) [27]:

Figure 3. A Pareto chart showing implementation models according to their citation frequencies. The bars, arranged in descending order to depict significance, show individual models and their citations; the line graph shows the cumulative total in percentage. (Calculations based on frequency of citations of publications citing each of the implementation models in 3 databases: PubMed, Web of Science and Google Scholar in the stated period). RE-AIM = Reach, Effectives, Adoption, Implementation and Maintenance; CFIR = Consolidated Framework for Implementation Research; PARIHS = Promoting Action in Research Implementation in Health Services; PRISM = Practical, Robust Implementation and Sustainability Model; CM-EBM = Conceptual Model of Evidence-based Practice Implementation in Public Service Sectors; KTE = Knowledge Translation and Exchange; NPT = Normalization Process Theory; ARC = Availability, Responsiveness & Continuity; AlFs = Availability Implementation Frameworks; SK = Sticky Knowledge; CM = Conceptual Model of Implementation Research.
### Table 2. Identified implementation frameworks, constructs, levels of analysis and publication sources

<table>
<thead>
<tr>
<th>Model</th>
<th>Associated Constructs</th>
<th>Levels of Analysis</th>
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<td>[31, 50-57]</td>
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<td></td>
<td>2. Adopter/implmenter/decision maker characteristics</td>
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<td>9. Cost</td>
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<td>12. Goals</td>
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<td>20. Relative advantage</td>
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<td>Implementation Effectiveness Model</td>
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<td>5. Context - Inner setting</td>
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<td>10. Outcomes - Implementation</td>
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<td>12. Strategies</td>
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<td>Knowledge Transfer and Exchange</td>
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<td>2. Barriers and facilitators</td>
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<td>Normalization Process Theory</td>
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<td>Organizational Theory of Innovation Implementation</td>
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<thead>
<tr>
<th>Framework</th>
<th>Components</th>
<th>Scope</th>
<th>References</th>
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</table>
| Promoting Action on Research Implementation in Health Services (PARIHS) | 1. Adoption  
2. Context - Inner setting  
3. Implementation  
4. Innovation characteristics  
5. Readiness | Individual Organization  
Community | [28, 29, 65-68] |
| Pronovost's 4E's Process Theory               | 1. Barriers and facilitators  
2. Engagement  
3. Evaluation  
4. Implementation  
5. Innovation characteristics  
6. Reach | Individual Organization  
Community | [69, 70] |
| Replicating Effective Programs Plus Framework | 1. Adaptation and evolution  
2. Communication channels  
3. Context - Inner setting  
4. Evaluation  
5. Fit  
6. Identification  
7. Implementation  
8. Maintenance and sustainability  
9. Pre-implementation | Organization  
Community | [71, 72] |
| Sticky Knowledge                              | 1. Implementation  
2. Maintenance and sustainability | Individual Organization  
Community | [73, 74] |
| Practical, Robust Implementation and Sustainability Model (PRISM)          | 1. Adoption  
2. Context - Inner setting  
3. Implementation  
4. Innovation characteristics  
5. Readiness | Individual Organization  | [30, 75] |
| Reach, effectiveness, adoption, implementation and maintenance (RE-AIM)    | 1. Reach  
2. Adoption  
3. Evaluation  
4. Implementation  
5. Maintenance and sustainability | Individual Organization  
Community | [76-86] |
I = R × E

PARIHS framework

Promoting Action on Research Implementation in Health Services (PARIHS) framework examines the interactions between the evidence, context and facilitation, the three intersecting elements that may influence PM implementation [28]. The model suggests that characteristics of an intervention (the what), the context or setting where the new evidence is to be implemented (the where) and how the implementation process is being facilitated (the how), all act to influence the implementation outcomes. Codified and non-codified sources of knowledge form the evidence. This evidence is divided into four source-based components: (a) research evidence from published sources, or formal experiments; (b) evidence from clinical experience (professional knowledge); (c) evidence from patient experiences and preferences (including those of caregivers and family); and (d) routine information derived from local practice context, which differs from professional experience in that it is the domain of the collective environment and not the individual [29]. The second component of PARIHS, facilitation, holds that one person makes things easier for others through support in helping others to change their attitudes, habits, skills, ways of thinking, and work. Implementation facilitation encompasses engaging both deliverers and recipients of the evidence to develop a common understanding about the benefits, disadvantages, risks and losses of the innovation. Facilitators work with individuals and teams to enhance the implementation process. Meanwhile, contexts differ and correspondingly affect implementation outcomes. Some contexts may be more conducive to the successful implementation of the evidence into practice than others, especially considering contextual factors as change champions, absorptive capacity of organizations and other elements of learning organizations and institutionalized evaluation mechanisms. Context is in three forms: culture (principles, values, beliefs, views, and attitudes among organizational members that are manifested at the group or organizational level, as well as among sub-units within the organization); leadership (teamwork, control, decision making, effectiveness of organizational structures, and issues related to empowerment) and evaluation (how organizational management deals with its own performance, and whether feedback is provided for within the organization). The framework can be summarized as:

\[ \text{SI} = f(\text{E}, \text{C}, \text{F}) \]

Where SI = successful implementation, E = evidence, C = context, F = facilitation and f = function of.

Each factor (evidence, context and facilitation) consists of sub-elements that can be rated on a scale from low to high where high ratings on each factor are more likely to produce successful implementation results [28, 29].

PRISM framework

The Practical, Robust Implementation and Sustainability Model (PRISM) focuses on intervention implementation based on multiple aspects of other implementation models including an expansion of RE-AIM [30]. The PRISM model considers determinant factors that influence implementation of an intervention and helps to measure implementation outcomes. PRISM focuses on the relationship between intervention design, external environment, organizational characteristics (implementation and sustainability infrastructure), and the intended recipient population. It seeks to demonstrate how an intervention interacts with recipients to influence adoption, implementation, maintenance, reach, and effectiveness.

CFIR framework

The Consolidated Framework for Implementation Research (CFIR) is primarily an implementation tool. It was designed to consolidate constructs drawn from pre-existing implementation theories to offer an overarching typology that can be used to conduct a diagnostic assessment of the implementation and context, track the progress of implementation, and explain the success (or lack of success) of an implementation strategy [31]. Various constructs contained in the CFIR model include: a) the characteristics of the intervention, such as its source, complexity, or cost; b) the outer setting, such as relevant governmental policies and regulations or external pressure that may influ-
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Although a complex process, PM implementation is aimed at enabling novel biomedical discoveries to efficiently, effectively and accurately get to clinical and public health settings in order to improve health outcomes. To achieve this, however, there are various factors that need to be well-thought-out. Careful consideration of these factors helps to simplify the process of managing implementation complexity. To support the creation and refinement of a PM implementation model therefore, we propose a six-factor implementation conceptual framework (Figure 4). It links implementation outcomes to biomedical research and clinician-patient interface settings, as well as to the wider health systems and the general public contexts. Factors involved include: a) the characteristics which underpin the efficacy and effectiveness of PM innovations; b) both near and distal contextual factors that constitute implementation barriers or facilitators; c) individuals that are involved in the implementation process (both providers and recipients); and d) the expected implementation outcomes. The identified constructs in Figure 4 can then be adapted and used as building blocks to study and test multi-level interrelationships among various hypothesized PM implementation vari-

![Figure 4. A precision medicine implementation conceptual framework illustrating six identified precision medicine factors and their constituent constructs.](image-url)
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Variables. Although constructs cannot be measured directly in observational studies, modern measurement approaches can be applied to quantify them [33].

The conceptual framework presented here provides a framework that may measure the effectiveness and efficiency of implementation processes. To this end, the conceptual model may be used in formulating and testing various hypotheses. Applying the framework may be central to evaluating not only determinants of implementation outcomes, but also in identifying stakeholders, selecting implementation strategies and mitigating implementation risks. For instance, the single or combined influence of the factors on observed and/or desired implementation outcomes can be hypothesized and tested. Based on the models identified in preceding sections therefore, this article discusses a range of factors that may interact at various levels of analysis (individual patient, care provider, interactions among professionals in teams, etc.) to influence PM implementation outcomes.

**Precision medicine implementation framework and the evidence base of omics biomarkers**

Although the interpretation and definition of clinically relevant genetic variation remains a challenge, clinical utility of omics biomarkers for the purposes of patient stratification has been prominent in the fields of pharmacogenomics [34, 35] and oncology [9] (Table 3). For instance, pharmacogenetic testing for human epidermal growth factor receptor type 2 (HER2) has been used to select patients with breast cancer who may benefit from trastuzumab and testing for the KRAS mutation to determine who is likely to benefit from therapies inhibiting the epidermal growth factor receptor (EGFR) [34].

Although inconclusive, the potential and feasibility for omics interventions to contribute to clinical care through PM has been demonstrated. Thus, the use of an OBM in clinical settings must have proven efficacy and effectiveness in the diagnosis, prognosis, or risk assessment of any disease or health status in individuals or populations. However, some studies have cast doubt on the clinical utility of omics-based interventions. One such study undertook a review to test for, among other evidence, the comparative effectiveness of testing for CYP2C19 genetic variants to guide antiplatelet therapy in coronary artery disease (clopidogrel) and CYP2D6 genetic variants to guide tamoxifen therapy for women at high risk for primary breast cancer or recurrence [9]. They concluded that there was limited evidence on the clinical utility of using genomic tests on health outcome. Another study on chromosomal mutation 9p21.3, which is associated with increased risk of cardiovascular disease in women, showed that knowledge of its presence adds no additional predictive power to the standard information on risk [36]. However, the apparent lack of evidence of clinical utility of genomic tests may be a methodological issue. Concerns have been raised regarding CER methodologies and whether they are commensurate with PM evidence [34]. For instance, with CER, groups of patients are analyzed to compare the effectiveness of alternative medical strategies, in order to advise clinical decisions and policies. This may contradict the very ideals of PM which stands for an approach to medical care that is based on unique individual characteristics rather than a collective, in order to select therapies biologically tailored to individual patient needs, such as customized monoclonal antibodies and vaccines. These are precisely the kinds of issues that implementation science methodologies can address. Well-designed studies using appropriate theoretical implementation models may be useful in broadening and deepening the fields of CER to adequately capture the clinical utility of PM interventions.

**Role of context in precision medicine implementation outcomes**

Differences in contexts (e.g., culture, health policies, healthcare organization characteristics) may explain variations in implementation outcomes of various healthcare innovations. A greater understanding of contextual factors and their characteristics is essential in deter-
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Table 3. Examples of clinical applications of omics biomarkers to guide treatment choices

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disease</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-kit</td>
<td>Gastrointestinal stromal tumor</td>
<td>Imatinib mesylate</td>
</tr>
<tr>
<td>CCR5</td>
<td>Human immunodeficiency virus</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Cytochrome P-450 variants</td>
<td>Various disorders</td>
<td>Warfarin, voriconazole</td>
</tr>
<tr>
<td>EGFR</td>
<td>Non-small-cell lung cancer</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>ALK</td>
<td>Cancer</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>HIV infection</td>
<td>Abacavir</td>
</tr>
<tr>
<td>IL28B</td>
<td>HCV infection</td>
<td>Pegylated interferon/ribavirin</td>
</tr>
<tr>
<td>HLA-B*1502</td>
<td>epilepsy, bipolar disorder</td>
<td>Carbamazepine</td>
</tr>
</tbody>
</table>

mining the effectiveness of PM implementation efforts. As illustrated in Figure 4, immediate and broader/distal contextual settings and the teams and individuals involved in PM implementation immensely influence implementation outcomes. These contextual features include community cultural beliefs, structural organizational characteristics (e.g., organizational complexity or financial status) and external factors (e.g., health regulations). In other words, some contexts are more likely to affect the effectiveness of PM implementation efforts than others.

Considering a contextual analysis for PM implementation is a complex undertaking. However, some contextual features may be amplified or diminished in significance depending on perceptions on the evidence backing omics biomarkers. Similarly, whether implementation of PM is being considered at national, hospital or unit level is important in assigning significance to some contextual features. For instance, some contextual features may be important for national public health pharmacogenomics as compared to unit-level, private hospital precision oncology.

**Precision medicine implementation and the immediate contextual setting: big data capability**

Individuals differ due to genetic, environmental and socioeconomic factors. Big data capabilities through omics and sensor technologies can now capture this human diversity with ease and precision [37]. Big data consists of extensive datasets—primarily in the characteristics of volume, variety, velocity, and/or variability—that require a scalable architecture for efficient storage, manipulation and analysis [38]. Through capturing high-resolution data about a person across molecular, environmental or behavioral parameters, big data analytics sheds light on obscured patterns, unidentified associations, as well as other insights to enable tailored diagnostic or therapeutic plans [39]. However, integrating and manipulating the data and turning it into exploitable knowledge for clinical decision making is a complex undertaking. Big data capability forms part of the immediate contextual settings that demonstrate organizational support for PM implementation. As the volume and variety of data grows, new and innovative means are needed to address and enable its optimal capture, integration, storage and redistribution. Big data approaches enable discovery of novel biomarkers such as single nucleotide variants (SNV) and point mutations that serve as therapeutic targets. However, novel applications and innovative assay concepts keep on emerging, bringing with them a host of challenges that create a daunting barrier to their application beyond research setting [40]. Technology fluidity due to constant improvements and upgrades to some data analytic platforms and algorithms not only creates difficulties in the choice of the most appropriate data analysis pipelines, but also puts a strain on organizational resources thereby affecting implementation outcomes.

Furthermore, it has been noted that one of the most ill-reputed challenges in genomics, hence PM, lies in the sheer number of databases and knowledge bases provided by the community and commercial vendors [40]. Therefore, keeping up with the latest databases, developing integration methods and tracking changes to formats can be a formidable challenge to adoption of PM interventions.

Data acquisition, quality control, integration, storage, and distribution are huge organization-
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al assignments that must be considered early when instituting PM implementation efforts. Figure 5 illustrates the importance of big data capabilities for successful PM implementation. Next generation sequencing (NGS) experiments generate massive files consisting of raw genomic data (FASTQ). Trimmed and cleaned FASTQ data files are then taken through secondary analysis to generate actionable knowledge, usually including alignment to a reference genome, de-novo assembly or k-mer counting [40]. Secondary analyses generate equally massive secondary and intermediate files describing the alignment, assembly or quantification of the raw data which are often sorted, filtered, annotated or analyzed in various ways.

Public engagement/education and precision medicine implementation

PM carries the promise of the right treatment at the right dose at the right time, with minimum adverse events and maximum efficacy. The routine use of genomics for disease prevention, diagnosis and treatment will require a better public and professional understanding of how individuals and their healthcare providers assimilate and use medical information. Due to the multi-parametric nature of genomic data, including both expected results and incidental findings out of genomic tests, new means of medical communication to both patients and health professionals is needed. This corresponds to the broader/distal contextual factors for successful implementation of interventions, as outlined in Figure 4. To address some characteristics of individuals and teams involved in PM implementation, effective clinical decision support tools and new educational models may be required.

Implementation science methodologies can greatly help PM interventions to be fully accessible to a wider population. For instance, development of novel and effective strategies for mobilizing bigger genomic study cohorts needed for generating PM evidence involving diverse stakeholder groups may be needed to maximize the relevance of genomics in health systems. Optimal models for targeting specific patient populations may leverage on imple-
Achieving better precision medicine outcomes through implementation science methodologies for efficiency and effectiveness.

Conclusion

This review has examined the main implementation science theories, models and frameworks and their salient features and constructs relevant to PM implementation. In summary, there is no one comprehensive model sufficiently appropriate for every angle of PM implementation research or practice. The models are not specifically operationalized for use in PM implementation. Therefore, there is need for to develop an appropriately operationalized PM implementation model that can be used by clinicians, the community, policy makers, and researchers to guide PM implementation in all its arrays. Such an approach will not only ensure that the PM firmly contributes sufficiently to improved health systems, but that there is an invigorated biomedical research agenda that is focused on systematically building a knowledge base across the translational science continuum that is highly relevant to PM interventions and improved health outcomes. Novel implementation models can be applied to overhaul the way OBM are discovered and applied, rather than following the traditional knowledge-discovery-utility process. The traditional implementation methods are overly oversimplified and have a supply-side bias, promoting a linear view that scientists come up with medical innovations which are then handed over to clinicians who, in turn, use them on patients. In the contrary, however, PM seeks to promote participation of research subjects.

To circumvent such linear thinking in OBM discovery and application, a cyclic feedback-looped process of OBM discovery is necessary. Moreover, a better coordination between wet laboratory (experimental), dry laboratory (bioinformatics) and implementation (clinical strategies), together with appropriately articulated multi-stakeholder engagement in the biomarker discovery process is essential. This calls for significant collaborative efforts across academic, industry (bio-pharmaceuticals) and regulatory authorities.

Study limitations

As this was a narrative review, our effort to gather all relevant implementation research theories, models and frameworks might have suffered from a lack of a more systematic search akin to systematic reviews. Despite our efforts to improve the consistency and clarity of the description of implementation theories relevant to PM, this review represents only a step toward achieving that goal. A broader search strategy that included non-English language sources may have revealed a greater number of theories and models too. However, our aim was not an attempt to be exhaustive, but to highlight the range of available implementation theories relevant to PM. We did not attempt to address geographical variations in relation to how different implementation models will relate to geo-economic variations such as LMICs and HICs, which deserve further attention in the literature. Thus, it is possible that some of the models and frameworks included in the review are more readily applicable to HICs like the U.K. health care systems. Nevertheless, we believe that most of the models included are broadly applicable.

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None.

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