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Personalized medicine: challenges and opportunities for translational bioinformatics

Casey Lynnette Overby[*,1] and **Peter Tarczy-Hornoch**[2,3,4]

[1]Program in Personalized & Genomic Medicine and Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[2]Department of Biomedical Informatics & Medical Education, University of Washington, Seattle, WA, USA

[3]Department of Pediatrics, University of Washington, Seattle, WA, USA

[4]Department of Computer Science & Engineering, University of Washington, Seattle, WA, USA

Abstract

Personalized medicine can be defined broadly as a model of healthcare that is predictive, personalized, preventive and participatory. Two US President's Council of Advisors on Science and Technology reports illustrate challenges in personalized medicine (in a 2008 report) and in use of health information technology (in a 2010 report). Translational bioinformatics is a field that can help address these challenges and is defined by the American Medical Informatics Association as "the development of storage, analytic and interpretive methods to optimize the transformation of increasing voluminous biomedical data into proactive, predictive, preventative and participatory health." This article discusses barriers to implementing genomics applications and current progress toward overcoming barriers, describes lessons learned from early experiences of institutions engaged in personalized medicine and provides example areas for translational bioinformatics research inquiry.

Keywords

biobanks; clinical decision support; computational analyses; education; electronic health records; implementation challenges; individual research results; personalized medicine; translational bioinformatics; translational research

The phrase 'personalized medicine' is commonly used to refer to genomic medicine; defined as "the use of information from genomes (from humans and other organisms) and their derivatives (RNA, proteins and metabolites) to guide medical decision-making" [1]. Personalized medicine may, however, be defined more broadly to be a model of healthcare that is predictive, personalized, preventive and participatory ('P4 Medicine') [2], and that also applies technologies to customize and deliver care [3]. Such a model in practice provides a venue for adopting genomics applications (i.e., genomic medicine) [4]. In September 2008, the US President's Council of Advisors on Science and Technology

[*]Author for correspondence: coverby@medicine.umaryland.edu.

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(PCAST) published their report on priorities for personalized medicine [101]. This report summarizes input from several stakeholders including healthcare providers, patients, academic scientists, policy makers, technology vendors, payors, and biopharmaceutical manufactures. In December 2010, PCAST released another report on the use of health information technology to improve healthcare that reiterated several of the informatics challenges in these areas [102]. It is important to note that although often the phrase personalized medicine and genomic medicine are often used interchangeably, in fact, personalized medicine is a superset and can include many nongenomic personalized screening and diagnostic approaches.

Both translational research (bringing basic discoveries into the clinical arena) and biomedical informatics (BMI) research can help provide solutions to many of the challenges highlighted by PCAST. BMI is defined as "the interdisciplinary field that studies and pursues the effective uses of biomedical data, information and knowledge for scientific inquiry, problem solving and decision-making, motivated by efforts to improve human health" [5]. BMI application areas support the transfer and integration of knowledge across the translational research continuum. At one end is bioinformatics (the development and application of computational tools to biological and biomedical research data) and at the other is public health informatics and population informatics. In between is clinical informatics, defined by American Medical Informatics Association (AMIA) as "the application of informatics and information technology to deliver healthcare services."

Translational research is required to integrate scientific discoveries into clinical practice, and has been described elsewhere as four iterative phases including: T1 research to develop candidate health applications (i.e., discovery research); T2 research to evaluate candidate application and develop evidence-based recommendations (i.e., guidance development); T3 research to assess how to integrate evidence-based recommendations into clinical care and prevention (i.e., implementation research and dissemination research); and T4 research to assess health outcomes and population impact (i.e., comparative effectiveness research) [6]. The bioinformatics application area has primarily focused in the T1 discovery research domain, however, phases that are most relevant to implementing personalized medicine are T2–T4 that aim to validate discoveries for use in practice, as well as create systems that can facilitate their use in clinical practice (e.g., pharmacogenomics decision support). A special issue of the *Journal of American Medical Informatics Association* describes a range of such studies and challenges the limited view of translational bioinformatics (TBI) as T1 research using molecular measurements to characterize disease [7].

The importance of the synergy between bio-informatics and clinical informatics was felt to be important enough that the theme of the 2002 AMIA Fall Symposium was 'Bio*Medical Informatics: One Discipline'. Subsequently, a special issue of the *Journal of Biomedical Informatics* was devoted to this theme [8]. Starting in 2008, the AMIA began holding its annual summit on TBI illustrating the application of BMI methods more broadly across the translational research continuum. TBI is described by AMIA as "the development of storage, analytic, and interpretive methods to optimize the transformation of increasing voluminous biomedical data into proactive, predictive, preventative, and participatory health" [9], demonstrating the explicit goal of TBI inquiry to affect clinical care. TBI has been described in more detail elsewhere as a distinctive domain of BMI [10-13,103].

In this article, we will discuss specific barriers to implementing genomics applications including: validating correlations between genetic markers and disease and identifying actionability; addressing concerns over the return of results and privacy that limit patient acceptance; educating patients and healthcare providers on the use and limitations of personalized medicine; and addressing the absence of robust scalable electronic health

record (EHR)-linked decision support tools. In doing so, we will discuss current progress to overcome barriers; lessons learned from the early experiences of institutions engaged in using genomic information in clinical care; and ways that TBI research and practice can help provide solutions. We will draw from a recent review article summarizing the successful experiences of approximately 20 groups brought together by the US NIH National Human Genome Research Institute (NHGRI) and who are 'early adopters' of genomic medicine [14]. Distinct from that article, we focus on understanding implementation challenges through TBI inquiry. We provide examples of challenges pursued by TBI researchers, including examples from our own experiences.

Validating genetic correlations & identifying actionability

The 2008 PCAST report on priorities for personalized medicine highlights that clinical validation of candidate genetic markers is proceeding at a slow pace, while the number of genetic markers being discovered continues to increase. Preanalytical factors including biospecimen collection, processing and storage can influence our ability to provide the reproducible scientific results necessary for validating genetic correlations. Thus efforts such as the NIH National Cancer Institute Biospecimen Research Network program are in place to better understand the effects of these activities and to improve upon quality [15]. Notable outcomes of these efforts include the National Cancer Institute Best Practices for Biospecimen Resources [104] and the Biospecimen Reporting for Improved Study Quality project that aims to strengthen communication and publications about biospecimen-related research [16]. Most relevant to TBI inquiry are the scientific analyses that occur after the biospecimen is acquired. For example, scientific analyses may employ computational methods in systems biology (an integrative approach to studying biological complexity). Systems biology involves the use of software tools at different stages of the computational workflow that involves data handling, network inference, deep curation, dynamic simulation and model analysis [17]. Print journals provide insufficient support for reproducible and reusable data and computational analyses [18,19]. As such, the Sage Bionetworks Commons' project is building a computational platform and data model repository, as well as establishing data sharing rules and policies for systems biology [20]. The European Molecular Biology Laboratory–European Bioinformatics Institute is coordinating a similar effort, ELIXIR [105], which will provide an infrastructure for managing biological data. There remain opportunities in TBI that build upon these efforts to develop community standards, to establish the infrastructure for sharing and to pursue research investigating the influence of computational workflow and analyses on the quality and reproducibility of findings.

While the belief that little has translated into clinical benefit continues to hold [21,22], there are now a number of genomics applications (e.g., family history [23,24] and pharmacogenomics [25,106]) with documented clinical validity and utility. Thus indicating the existence of barriers other than clinical validation. Barriers are beginning to be explored in programs such as the Electronic Medical Records and Genomics (eMERGE) Network [26], the Pharmacogenomics Research Network (PGRN), Translational Pharmacogenomics Program (TPP) [27,107], the NIH NHGRI Clinical Sequencing Exploratory Research (CSER) [108] and Return of Results (ROR) [109] consortia. Early experiences implementing genomics applications indicate that identifying the actionability for specific variants is a challenge given the complexity of generating and evaluating evidence [14]. The evidence, and ultimately the actionability, of specific gene variants changes over time and sometimes is not clear cut. Efforts to formalize evidence evaluation approaches include the US CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group [28] and the Clinical Pharmacogenetics Implementation Consortium [25]. This process, however, is manual, requiring a large amount of time and effort from experts.

There may be opportunities in TBI to explore more automated approaches to evaluate scientific evidence and assist with this process. There are already some published works that leverage existing resources (e.g., PharmGKB [110] and MEDLINE [111]) to perform automatic summarization of information [29-31] and computational reasoning [32,33]. NIH NHGRI is funding a number of grants both under their CSER initiative [108] and their ROR consortium [109] that focus on both the area of identifying actionability, as well as developing decision support tools.

Addressing concerns over the return of results & privacy

The collection, processing and analysis of bio-specimen also raise ethical, legal and social issues regarding accessibility. For example, there is considerable controversy around returning individual results and biobanks that provide long-term storage of biospecimen for research or clinical purposes [34,35]. The controversy has often been around returning incidental findings to study participants. With the emergence of biobank-linked EHRs, returning results during routine clinical care can now be explored. One relevant study reports experiences from the eMERGE Network that consists of institutions and genotyping centers conducting genome-wide association studies using phenotypes derived from the EHR [36]. The authors consider three classes of research findings that could warrant reporting (genotypes associated with Klinefelter syndrome, Turner syndrome and factor V Leiden), and review EHR data for affected participants at the network sites. That review suggested most participants were likely unaware of their genotype, highlighting the potential benefit of returning findings. For many conditions, however, the designation of what is clinically actionable is less straightforward and the potential benefit hinges on the validity of the genetic correlations. For example, the threshold for what is a valid correlation differs depending on whether we are using genomics data for screening purposes or diagnosis purposes. A threshold that is not stringent enough in either case can lead to large number of incidental findings (i.e., false-positive results) that can result in cascade effects (or the chain of events initiated by an unexpected result that leads to unnecessary additional testing or treatments [37]). Cascade effects may lead to unnecessary cause for concern by the patient, potential harm to a patient due to inappropriate treatment and excessive healthcare expenditures. In light of these concerns we foresee additional demands on already burdened clinical geneticists and genetic counselors to assist with individualized interpretation of test results. Such interpretation of human genomes will be complex, particularly in the face of what has been termed the ‘incidentalome’ [38,39]. Relevant areas for TBI inquiry may include investigating automation and tailoring of test interpretation and communication for healthcare providers and patients to mitigate this burden. There is much enthusiasm in this arena with events such as Boston Children’s Hospital’s 2012 CLARITY (Clinical Genome Interpretation) Challenge involving 23 academic and commercial organizations representing ten countries [112]. The diverse involvement of academic and commercial organizations also illustrates growing opportunities for industry–academic partnerships in TBI research.

Other concerns related to returning results are due to the increased risk of unintended release of identifying information, and difficulties preserving individual privacy in correlating genetic signatures with disease. These concerns include the potential stigmatizing effects of discovering a population or patients’ susceptibility to a disease or condition, and risks of these data being used wrongly by insurance companies or employers. In the USA, the Health Insurance Portability and Accountability Act of 2006 (PL-104-191) [40], the amended Americans with Disabilities Act of 1990 (PL-110-325) [41] and the Genetic Information Nondiscrimination Act (GINA) of 2008 (PL-110-223) [42] begin to address some of these issues. BMI research and practice can also provide approaches to safeguard against these concerns. The National Research Council, for example, proposes technical solutions and data safety practices [43]. Security functions include ensuring:

- Availability (ensure that accurate and up-to-date information is available);
- Accountability (ensure that users are responsible for their access to and use of information);
- Perimeter (control the boundaries of trusted access to an information system);
- Role-limited access (restrict access for personnel to information that is essential to their jobs);
- Comprehensibility and control (ensure that record owners understand different aspects of information control, confidentiality and access).

Specific steps to support these functions include:

- The use of audit trails to support accountability for use of medical data;
- The use of encryption and password protection to prevent access to information outside of the intended audience;
- The use of transaction-specific access codes to facilitate role-limited access.

There are examples of published methods for ensuring privacy or anonymity of biomedical data [44,45]. Although these technical safeguards provide tools for protecting electronic information, in order to truly participate in practices that protect the privacy and confidentiality of individuals, standard operating procedures must be in place. Such practices and procedures are likely to vary with biobanks given the reported diversity in the organizational structures [46]. While the number of documented cases of discrimination on the basis of genetic test results is currently small [113], as connecting biobanks with EHRs become more prevalent its important to include functions such as those put forth by the National Research Council to facilitate uncovering and documenting discriminatory use of data.

Related to returning results, there also needs to be an infrastructure in place to facilitate more fine-grained individual privacy preferences. PCAST recommends adopting a universal exchange language for healthcare information to do this and to facilitate implementing privacy rules across institutions. While there are some examples of such infrastructures (e.g., Private Access™, Inc. [114] and the NIH Biomedical Translational Research Information System [47,115]), there are few formal demonstration studies of their success to date thus providing another area for TBI inquiry. With the appropriate privacy protections and infrastructure for selecting privacy preferences, patients will be able to benefit from better diagnosis and treatment options that depend on their specific personal histories and clinical data, including genetics data.

Educating patients & healthcare providers

As mentioned earlier, there are concerns regarding the demands on clinical geneticists and genetic counselors. Education and training for the clinical care professionals outside of these specialties is also a recognized need [116,117]. For nonspecialists, competencies of focus may include recognizing when a genetic or genomic test is needed or how pharmacogenomic testing can guide decisions about therapy [117]. Processes to facilitate collaborative partnerships between disciplines [48] and with patients will be important to implement genomics applications, although this will not be straight forward. The traditional model is to use and communicate genetic or genomic information during ‘teachable moments’ following diagnosis [49]. However this model may not be appropriate for complex conditions affecting a large portion of the population with moderate or lower increases in risk (e.g., cancer and diabetes) [117]. A collaborative model involving health professionals, medical librarians, laboratories and the public should be explored. Areas of

TBI inquiry to investigate such a model might include observing current workflow and referral processes to identify areas for point-of-care decision support for collaborative activities. In addition TBI methods might be employed to make knowledge for personalized medicine more readily available through the design and creation of electronic knowledge resources. There are currently freely available resources such as the Genetics Home Reference [118] that present information about the relation between genetics and disease in a format that may be understood by a lay audience. Knowledge resources geared more towards a clinical audience include the Gene Tests/Gene Reviews Knowledge Base [50,51,119] and the Genetic Testing Registry [120]. As an important caveat, such resources should provide up-to-date and accurate information, in a form that supports the questions of the intended audience. One way to ensure that resources are at an acceptable level of usefulness is to involve potential users of the system in the design and evaluation processes.

Some institutions have chosen to create customized educational materials as part of their personalized medicine programs. Two such programs include St Jude Children's Research Hospital Pharmacogenomics of Anticancer Agents Research 4Kids (PG4Kids) program [121] and the Icahn School of Medicine at Mount Sinai Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics – Pharmacogenomics (CLIPMERGE PGx) program [52]. Both programs aim to migrate preemptive pharmacogenetic dosing guidelines into routine patient care. The CLIPMERGE PGx program includes an education component as part of their recruitment process. Before enlisting in the project, providers must attend a 30-min presentation outlining the aims, scientific justification and the clinical decision support (CDS) content to be presented if they decide to participate. The PG4Kids project provides open access to an educational video that provides information for families [122]. In addition, the program website lists genes they test and that are reportable, and with links to more detailed information for clinicians. There remain opportunities for TBI scientific inquiry to understand the influence of these educational interventions on uptake and perceptions of genomics applications, and downstream clinical outcomes. Another area of TBI inquiry is in the development and maintenance of genomics knowledge bases to make educational materials available to providers at the point of care via CDS embedded in the EHR. Given the huge amount of genomics knowledge, curation of such knowledge bases by an individual institution will not scale. Managing continually updated, expert-authored, peer-reviewed, computable, evidence-based knowledge will be key to establishing scalable solutions for genomics knowledge (including educational materials).

Establishing EHR-linked decision support tools

CDS brings relevant information, filtered or presented to clinicians at particular times, to enable optimal care [53]. Embedding CDS in the EHR is recognized as promising to support personalized medicine [54-56]. There are currently, however, few deployed EHRs that have implemented genomic CDS. Some limitations are due to the lack of decision support functionality and lack of a platform for innovative applications in EHRs [102]. Our previous work designing and developing a prototype pharmacogenomics CDS system that builds on existing clinical infrastructure illustrates limitations due to the maturity of genomics knowledge and in clinical system CDS capabilities [57,58].

We used characteristics of pharmacogenomics knowledge derived from US FDA drug labels to inform the design of a conceptual model for pharmacogenomics CDS. We also analyzed the functional requirements and capabilities of local clinical systems to support pharmacogenomics CDS. We found that the maturity of pharmacogenomics knowledge in FDA drug labels varied such that there is a need for semiactive configurations, such as context-specific links to websites, and active configurations of CDS, such as automated alert

messages. That is, active configurations are better suited for more mature or actionable knowledge compared with less mature knowledge. Our local clinical systems did not directly support semiactive forms of CDS at the time this study was conducted, which also illustrated the need for a platform for innovation. Given our use of Cerner® (Cerner Corporation, MO, USA) products, the Cerner MPages™ (Cerner Corporation) technology that allows for customizable development might be leveraged to overcome some barriers [57]. The Substitutable Medical Apps Reusable Technologies (SMART) platform is another technology for integrating with EHRs that is open source [59]. It defines an application programming interface and provides software to facilitate access to data in a standardized format. Such technologies might provide a venue for incorporating new approaches as well as previously developed approaches (e.g., LifeLines [60]) to visualize biomedical data in EHRs.

Another limitation for personalized medicine in particular, is that much of the data for executing decision support may not be available currently in the EHR. CDS is 'triggered' by events such as storing a laboratory result or entering an order. Our study indicated that sufficient clinical data existed in our local EHR to support, or trigger, 50% of genomics decision support rules derived from FDA drug labels [58]. An EHR infrastructure that provides appropriate access to discrete data for CDS implementation is required. Information extracted from the notes using parsing and natural language processing techniques may also contribute to CDS systems in the EHR [61]. On the policy level, there are recent initiatives by the Office of the National Coordinator for Health Information Technology (ONC) to promote the adoption of EHR technologies (including CDS technologies) connected through a national health information network. The ONC specifies criteria for 'meaningful use' of EHRs to be eligible for the Health Information Technology for Economic and Clinical Health (HITECH) Act incentive payments through Medicare and Medicaid. Demonstrating use of decision support tools is a prominent requirement for meaningful use:

- Stage 1, which took effect in 2011, specified implementation of CDS;
- Stage 2, taking effect in 2013, specifies use of CDS to improve performance;
- Stage 3, taking effect in 2015, will require demonstrated use of CDS in ways that improve the outcomes of care.

Of particular relevance to personalized medicine are the Stage 2 criteria to record patient family health history as structured data, and to adopt the Health Level Seven (HL7) Context Aware Knowledge Retrieval Standard that supports integration of Infobuttons for semiactive CDS [62].

The Infobutton Manager is a technology for managing biomedical content [63]. It is accessed through a clinical information system, anticipates clinician's questions and provides links to relevant electronic resources [64]. OpenInfobutton is an open source platform for Infobutton that is compatible with the HL7 standard [65,123]. In addition to OpenInfobutton, another open source platform that may be used for sharing genomics content is the OpenCDS tools and resources project [124]. OpenCDS interfaces with WarfarinDosing.org [125], for example, to provide content relevant for personalized medicine. Content includes patient-specific warfarin dosing recommendations given both clinical and genetics data [66]. As mentioned in the previous section, managing genomics knowledge is particularly challenging. Technologies such as OpenInfobutton and OpenCDS illustrate progress toward establishing scalable solutions. While CDS is a promising approach to facilitate personalized medicine, there are few studies to date investigating design, implementation and evaluation of CDS for personalized medicine indicating great opportunities for TBI research [67]. Of particular importance in evaluations is use of

surveillance approaches to assess the clinical impact of CDS on an ongoing basis. TBI investigators might draw from 'Phase IV' clinical trials, or postapproval, study designs to assess whether CDS interventions for personalized medicine are improving care. Like with Phase IV clinical trials, we cannot assume based on preliminary data that the impact of an intervention will be positive once it is put into use.

Future perspective

There is a need for new clinical care delivery models for personalized and genomic medicine, and translational research has the potential to facilitate such models. There are estimates, however, suggesting no more than 3% of translational research efforts aim to validate genomic discoveries for use in practice (T2–T4 research) [6]. TBI is a growing domain of BMI that shows great promise to fill these gaps. As we move to more personalized health care, TBI research will be necessary to address challenges to validating genetic marker–disease correlations and identifying actionability, returning study results to patients, insuring privacy of patient data, educating patients and healthcare providers on the use and limitations of personalized medicine, and incorporating decision support tools in EHRs to support personalized medicine. Throughout this article we have provided examples of TBI areas of inquiry to help understand and address these challenges.

In the coming years we expect the TBI workforce to expand in the US given the growing number of institutional awards supported by the NIH National Center for Advancing Translational Sciences (NCATS)clinical and translational science award (CTSA) program, and growing emphasis in TBI training among NIH National Library of Medicine University-based Biomedical Informatics Research Training Programs. The CTSA program recognizes that investigators from diverse disciplines, BMI among them, are required for effective translational research [68,69]. As such, institutional CTSAs are beginning to provide support for TBI training (e.g., Boston University Clinical and Translational Science Institute TBI Program [126]). National Library of Medicine training programs also support TBI training with 18 of the 20 funded programs that list TBI as an area of emphasis [127]. We also expect more balanced contributions along the translational research continuum due to TBI contributions as research funding for TBI continues to increase. Between 1995 and 2007 the number of NIH-issued request for applications and program announcements with the word 'informatics' trended upward with 136 mentions in 2007 [11]. Last, we believe that TBI will help fuel the disruptive innovation needed to advance personalized medicine to standard of care. There are, for example, several medications with bio-marker-associated risks that are not considered in standard care practices but are described in the FDA labeling. Manufacturers compose drug labeling to market their product and to inform consumers of the associated risks, thus, information in its current form may not be appropriate or accessible for use by prescribing physicians. TBI research can help facilitate personalized medicine practices such as biomarker-informed prescribing by designing, implementing and evaluating new and creative techniques and technologies.

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References

Papers of special note have been highlighted as:

■ of interest

1. Olson, S.; Beachy, SH.; Giammaria, CF.; Berger, AC. Integrating Large-Scale Genomic Information into Clinical Practice. The National Acadamies Press; Washington, DC, USA: 2012.
2. Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. N Biotechnol. 2012; 29(6):613–624. [PubMed: 22450380]
3. Snyderman R. Personalized health care: from theory to practice. Biotechnol J. 2012; 7(8):973–979. [PubMed: 22180345]
4. Burnette R, Simmons LA, Snyderman R. Personalized health care as a pathway for the adoption of genomic medicine. J Pers Med. 2012; 2(4):232–240.
5. Kulikowski CA, Shortliffe EH, Currie LM, et al. AMIA Board white paper: definition of biomedical informatics and specification of core competencies for graduate education in the discipline. J Am Med Inform Assoc. 2012; 19(6):931–938. [PubMed: 22683918]
6. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? Genet Med. 2007; 9(10):665–674. [PubMed: 18073579]
7. Butte AJ, Ohno-Machado L. Making it personal: translational bioinformatics. J Am Med Inform Assoc. 2013; 20(4):595–596. [PubMed: 23757438]
8■. Tarczy-Hornoch P, Markey MK, Smith JA, Hiruki T. Bio*medical informatics and genomic medicine: research and training. J Biomed Inform. 2007; 40(1):1–4. Illustrates the synergy between bioinformatics and clinical informatics. [PubMed: 18239725]
9. Lorenzi NM. AMIA's realigned strategic plan. J Am Med Inform Assoc. 2011; 18(2):203–208. [PubMed: 21385825]
10. Altman RB. Translational bioinformatics: linking the molecular world to the clinical world. Clin Pharmacol Ther. 2012; 91(6):994–1000. [PubMed: 22549287]
11. Butte AJ. Translational bioinformatics: coming of age. J Am Med Inform Assoc. 2008; 15(6):709–714. [PubMed: 18755990]
12. Sarkar IN. Biomedical informatics and translational medicine. J Transl Med. 2010; 8:22. [PubMed: 20187952]
13■. Sarkar IN, Butte AJ, Lussier YA, Tarczy-Hornoch P, Ohno-Machado L. Translational bioinformatics: linking knowledge across biological and clinical realms. J Am Med Inform Assoc. 2011; 18(4):354–357. Presents translational bioinformatics as a discipline that bridges biological and clinical knowledge. [PubMed: 21561873]
14■. Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. Genet Med. 2013; 15(4):258–267. Describes early experiences implementing genomic medicine in the clinic. [PubMed: 23306799]
15. Moore HM. The NCI biospecimen research network. Biotech Histochem. 2012; 87(1):18–23. [PubMed: 21745162]
16. Moore HM, Kelly AB, Jewell SD, et al. Biospecimen reporting for improved study quality (BRISQ). J Proteome Res. 2011; 10(8):3429–3438. [PubMed: 21574648]
17. Ghosh S, Matsuoka Y, Asai Y, Hsin KY, Kitano H. Software for systems biology: from tools to integrated platforms. Nat Rev Genet. 2011; 12(12):821–832. [PubMed: 22048662]
18. Mesirov JP. Computer science. Accessible reproducible research. Science. 2010; 327(5964):415–416. [PubMed: 20093459]
19. Ioannidis JP, Allison DB, Ball CA, et al. Repeatability of published microarray gene expression analyses. Nat Genet. 2009; 41(2):149–155. [PubMed: 19174838]
20. Derry JM, Mangravite LM, Suver C, et al. Developing predictive molecular maps of human disease through community-based modeling. Nat Genet. 2012; 44(2):127–130. [PubMed: 22281773]
21. Varmus H. Ten years on – the human genome and medicine. N Engl J Med. 2010; 362(21):2028–2029. [PubMed: 20505183]

22. Evans JP, Meslin EM, Marteau TM, Caulfield T. Genomics. Deflating the genomic bubble. Science. 2011; 331(6019):861–862. [PubMed: 21330519]

23. Qureshi N, Armstrong S, Dhiman P, et al. Effect of adding systematic family history enquiry to cardiovascular disease risk assessment in primary care: a matched-pair, cluster randomized trial. Ann Intern Med. 2012; 156(4):253–262. [PubMed: 22351711]

24. Rubinstein WS, Acheson LS, O'Neill SM, et al. Clinical utility of family history for cancer screening and referral in primary care: a report from the family healthware impact trial. Genet Med. 2011; 13(11):956–965. [PubMed: 22075527]

25. Relling MV, Klein TE. CPIC. Clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin Pharmacol Ther. 2011; 89(3):464–467. [PubMed: 21270786]

26. McCarty CA, Chisholm RL, Chute CG, et al. The eMERGE Network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. BMC Med Genomics. 2011; 4:13. [PubMed: 21269473]

27. Shuldiner AR, Relling MV, Peterson JF, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. Clin Pharmacol Ther. 2013 Epub ahead of print. 10.1038/clpt.2013.59

28. Teutsch SM, Bradley LA, Palomaki GE, et al. The evaluation of genomic applications in practice and prevention (EGAPP) initiative: methods of the EGAPP working group. Genet Med. 2009; 11(1):3–14. [PubMed: 18813139]

29. Fiszman M, Rindflesch TC, Kilicoglu H. Summarizing drug information in medline citations. AMIA Annu Symp Proc. 2006:254–258. [PubMed: 17238342]

30. Tari L, Anwar S, Liang S, Hakenberg J, Baral C. Synthesis of pharmacokinetic pathways through knowledge acquisition and automated reasoning. Pac Symp Biocomput. 2010; 15:465–476. [PubMed: 19908398]

31. Yang J, Cohen A, Hersh W. Evaluation of a gene information summarization system by users during the analysis process of microarray datasets. BMC Bioinformatics. 2009; 10(Suppl. 2):S5. [PubMed: 19208193]

32. Boyce R, Collins C, Horn J, Kalet I. Computing with evidence Part I: a drug-mechanism evidence taxonomy oriented toward confidence assignment. J Biomed Inform. 2009; 42(6):979–989. [PubMed: 19435613]

33. Overby CL, Devine EB, Tarczy-Hornoch P, Kalet IJ. Deriving rules and assertions from pharmacogenomics knowledge resources in support of patient drug metabolism efficacy predictions. J Am Med Inform Assoc. 2012; 19(5):840–850. [PubMed: 22539082]

34. Wolf SM, Crock BN, Van Ness B, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med. 2012; 14(4):361–384. [PubMed: 22436882]

35. Parks A. 10 ideas changing the world right now: biobanks. Time. Mar 12.2009

36. Fullerton SM, Wolf WA, Brothers KB, et al. Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) network. Genet Med. 2012; 14(4):424–431. [PubMed: 22361898]

37. Deyo RA. Cascade effects of medical technology. Annu Rev Public Health. 2002; 23:23–44. [PubMed: 11910053]

38. Kohane IS, Hsing M, Kong SW. Taxonomizing, sizing, and overcoming the incidentalome. Genet Med. 2012; 14(4):399–404. [PubMed: 22323072]

39■. Kohane IS, Masys DR, Altman RB. The incidentalome: a threat to genomic medicine. JAMA. 2006; 296(2):212–215. Describes the potential for discovering multiple abnormal findings with use of large-scale genomic technologies. [PubMed: 16835427]

40. The Health Insurance Portability and Accountability Act of 1996 (HIPAA). Public Law 104–191, 110 Stat 1936. 1996

41. Americans with Disabilities Amendments Act of 1990 (ADAAA). Public Law 110–325, 122 Stat 3553. 2008

42. Genetic Information Nondiscrimination Act of 2008 (GINA). Public Law 110–233, 122 Stat 881. 2008

43. Clayton, PD.; Boebert, WE.; Defriese, GH., et al. For The Record: Protecting Electronic Health Information. National Research Council The National Academy Press; Washington, DC, USA: 1997.
44. Heatherly RD, Loukides G, Denny JC, Haines JL, Roden DM, Malin BA. Enabling genomic-phenomic association discovery without sacrificing anonymity. PLoS ONE. 2013; 8(2):e53875. [PubMed: 23405076]
45. Malin B, Sweeney L. How (not) to protect genomic data privacy in a distributed network: using trail re-identification to evaluate and design anonymity protection systems. J Biomed Inform. 2004; 37(3):179–192. [PubMed: 15196482]
46. Henderson GE, Cadigan RJ, Edwards TP, et al. Characterizing biobank organizations in the U.S.: results from a national survey. Genome Med. 2013; 5(1):3. [PubMed: 23351549]
47. Cimino JJ, Ayres EJ. The clinical research data repository of the US National Institutes of Health. Stud Health Technol Inform. 2010; 160(Pt 2):1299–1303. [PubMed: 20841894]
48. Korf BR. Genetics training in the genomic era. Curr Opin Pediatr. 2005; 17(6):747–750. [PubMed: 16282781]
49. Lawson PJ, Flocke SA. Teachable moments for health behavior change: a concept analysis. Patient Educ Couns. 2009; 76(1):25–30. [PubMed: 19110395]
50. Pagon RA. GeneTests: an online genetic information resource for health care providers. J Med Libr Assoc. 2006; 94(3):343–348. [PubMed: 16888670]
51. Pagon RA, Tarczy-Hornoch P, Baskin PK, et al. GeneTests–GeneClinics: genetic testing information for a growing audience. Hum Mutat. 2002; 19(5):501–509. [PubMed: 11968082]
52. Gottesman O, Scott SA, Ellis SB, et al. The CLIPMERGE PGx program: clinical implementation of personalized medicine through electronic health records and genomics – pharmacogenomics. Clin Pharmacol Ther. 2013 In Press.
53. Teich JM, Osheroff JA, Pifer EA, Sittig DF, Jenders RA. Clinical decision support in electronic prescribing: recommendations and an action plan: report of the joint clinical decision support workgroup. J Am Med Inform Assoc. 2005; 12(4):365–376. [PubMed: 15802474]
54. Brinner KA, Downing GJ. Advancing patient-centered pediatric care through health information exchange: update from the American Health Information Community Personalized Health Care Workgroup. Pediatrics. 2009; 123(Suppl. 2):S122–S124. [PubMed: 19088228]
55. Kawamoto K, Lobach DF, Willard HF, Ginsburg GS. A national clinical decision support infrastructure to enable the widespread and consistent practice of genomic and personalized medicine. BMC Med Inform Decis Mak. 2009; 9:17. [PubMed: 19309514]
56. Hoffman MA, Williams MS. Electronic medical records and personalized medicine. Hum Genet. 2011; 130(1):33–39. [PubMed: 21519832]
57. Overby CL, Tarczy-Hornoch P, Kalet IJ, et al. Developing a prototype system for integrating pharmacogenomics findings into clinical practice. J Pers Med. 2012; 2(4):241–256. [PubMed: 23741623]
58. Overby CL, Tarczy-Hornoch P, Hoath JI, Kalet IJ, Veenstra DL. Feasibility of incorporating genomic knowledge into electronic medical records for pharmacogenomic clinical decision support. BMC Bioinformatics. 2010; 11(Suppl. 9):S10. [PubMed: 21044357]
59. Mandl KD, Mandel JC, Murphy SN, et al. The SMART platform: early experience enabling substitutable applications for electronic health records. J Am Med Inform Assoc. 2012; 19(4):597–603. [PubMed: 22427539]
60. Plaisant C, Mushlin R, Snyder A, Li J, Heller D, Shneiderman B. LifeLines: using visualization to enhance navigation and analysis of patient records. Proc AMIA Symp. 1998:76–80. [PubMed: 9929185]
61. Demner-Fushman D, Chapman WW, McDonald CJ. What can natural language processing do for clinical decision support? J Biomed Inform. 2009; 42(5):760–772. [PubMed: 19683066]
62. Office of the National Coordinator for Health Information Technology (ONC), Department of Health and Human Services. Health information technology: standards, implementation specifications, and certification criteria for electronic health record technology, 2014 edition; revisions to the permanent certification program for health information technology. Final rule. Fed Regist. 2012; 77(171):72985–72991. [PubMed: 23227573]

63. Cimino JJ, Li J, Bakken S, Patel VL. Theoretical, empirical and practical approaches to resolving the unmet information needs of clinical information system users. AMIA Annu Symp. 2002:170–174.

64. Collins SA, Currie LM, Bakken S, Cimino JJ. Information needs, Infobutton Manager use, and satisfaction by clinician type: a case study. J Am Med Inform Assoc. 2009; 16(1):140–142. [PubMed: 18952943]

65. Del Fiol G, Huser V, Strasberg HR, Maviglia SM, Curtis C, Cimino JJ. Implementations of the HL7 context-aware knowledge retrieval ('Infobutton') standard: challenges, strengths, limitations, and uptake. J Biomed Inform. 2012; 45(4):726–735. [PubMed: 22226933]

66. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther. 2008; 84(3):326–331. [PubMed: 18305455]

67■. Welch BM, Kawamoto K. Clinical decision support for genetically guided personalized medicine: a systematic review. J Am Med Inform Assoc. 2013; 20(2):388–400. Review of the literature on clinical decision support for genetically guided personalized medicine. [PubMed: 22922173]

68. Bernstam EV, Hersh WR, Johnson SB, et al. Synergies and distinctions between computational disciplines in biomedical research: perspective from the clinical and translational science award programs. Acad Med J Assoc Am Med Coll. 2009; 84(7):964.

69. Zerhouni EA. Translational research: moving discovery to practice. Clin Pharmacol Ther. 2007; 81(1):126–128. [PubMed: 17186011]

Websites

101■. President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. 2008. www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf US government report describing challenges in personalized medicine

102■. President's Council of Advisors on Science and Technology. Report to the President: realizing the full potential of health information technology to improve healthcare for all Americans: the path forward. 2010. www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-health-it-report.pdf US government report describing challenges for health information technology

103. PLoS Computational Biology Translational Bioinformatics collection. www.ploscollections.org/translationalbioinformatics

104. US NIH NCI. NCI Best Practices for Biospecimen Resources. http://biospecimens.cancer.gov/bestpractices

105. ELIXIR. www.elixir-europe.org

106. US FDA. Table of valid genomic biomarkers in the context of approved drug labels. www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

107. The Pharmacogenomics Research Network. http://pgrn.org

108. US NIH NHGRI. Clinical Sequencing Exploratory Research Research Program. www.genome.gov/27546194

109. US NIH NHGRI. NHGRI funds return of results studies, forms expert consortium. www.genome.gov/27545526

110. The Pharmacogenomics Knowledge Base (PharmGKB). www.pharmgkb.org

111. NIH National Library of Medicine. MEDLINE®/PubMed® Resources Guide. www.nlm.nih.gov/bsd/pmresources.html

112. CLARITY Challenge – Boston Children's Hospital. http://genes.childrenshospital.org

113. Presidential Commission for the Study of Bioethical Issues. PRIVACY and PROGRESS in Whole Genome Sequencing. Oct. 2012 www.bioethics.gov/cms/sites/default/files/PrivacyProgress508.pdf

114. PrivateAccess, Inc.; www.privateaccess.info

115. BTRIS: NIH Biomedical Translational Research Information System. http://btris.nih.gov

116. AAMC–HHMI Scientific Foundations for Future Physicians. 2009. www.hhmi.org/grants/pdf/08-209_AAMC-HHMI_report.pdf

117■. US Secretary's Advisory Committee on Genetics, Health, and Society. Genetics Education and Training. Feb. 2011 http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_education_report_2011.pdf US government report describing current research and recommendations for improving genetics education

118. US NIH NLM. Genetics Home Reference. http://ghr.nlm.nih.gov

119. GeneReviews at GeneTests: Medical Genetics Information Resource. University of Washington; www.genetests.org

120. US NIH NCBI. Genetic Testing Registry. www.ncbi.nlm.nih.gov/gtr

121. St Jude Children's Research Hospital. Non-Therapeutic Protocol, PG4KDS: Clinical Implementation of Pharmacogenetics. www.stjude.org/pg4kds

122. St Jude Children's Research Hospital. St Jude's Family Advisory Council: PGEN4Kids Study Information. 2012. https://s.stjude.org/multimedia/PG4KDS/PGEN4Kid.html

123. OpenInfobutton project. www.openinfobutton.org

124. Open Clinical Decision Support (OpenCDS) tools and resources. www.opencds.org

125. Warfarin Dosing. http://warfarindosing.org

126. Clinical and Translational Science Institute, Boston University. Biomedical Informatics. http://ctsi.bu.edu/index.php/programs/biomedical-informatics/#TB

127. US NIH NLM. NLM's University-based Biomedical Informatics Research Training Programs. www.nlm.nih.gov/ep/GrantTrainInstitute.html

Executive summary

Background

- The US President's Council of Advisors on Science and Technology published two reports highlighting challenges for personalized medicine (in 2008) and challenges for use of health information technology (in 2010).
- Translational bioinformatics (TBI) is a domain of biomedical informatics that can help address challenges reported by the President's Council of Advisors on Science and Technology.

Validating genetic correlations & identifying actionability

- Clinical validation of candidate genetic markers is proceeding at a slow pace.
- Actionability of specific gene variants changes over time and sometimes is not clear cut.
- Relevant areas for TBI inquiry to address challenges and concerns include investigating approaches to support reproducible and reusable data and computational analyses; and to provide more automated approaches to evaluate scientific evidence and assist with the review process.

Addressing concerns over return of results & privacy

- The collection, processing and analysis of biospecimen raises ethical, legal and social issues regarding accessibility.
- There are concerns regarding privacy in clinical correlation of genetic variation with disease.
- Relevant areas for TBI inquiry to address challenges and concerns include investigating approaches to automate and tailor test interpretation and communication for healthcare providers and patients; insuring privacy with use of technology; and demonstrating the value of infrastructures to facilitate individual privacy preferences.

Educating patients & healthcare providers

- There are concerns regarding the high demand for assistance with individual interpretation of test results.
- Relevant areas for TBI inquiry to address challenges and concerns include investigating current workflow and referral processes to identify areas for point-of-care decision support for collaborative activities; making knowledge for personalized medicine more readily available through the design and creation of knowledge resources; and investigating the influence of educational interventions on uptake and perceptions of genomics applications, and downstream clinical outcomes.

Establishing electronic health record-linked decision support tools

- Few deployed electronic health records to date have implemented genomic clinical decision support.
- Relevant areas for TBI inquiry to address challenges and concerns include investigating design, implementation and evaluation of clinical decision support for personalized medicine; and establishing scalable solutions for managing clinical decision support knowledge for personalized medicine.

Future perspective

- We expect the TBI workforce to expand in the USA given the growth in training programs.
- We expect more balanced contributions along the translational research continuum due to TBI contributions.
- We believe TBI will help fuel the disruptive innovation needed to advance personalized medicine to standard of care.