Perspective

For reprint orders, please contact: reprints@futuremedicine.com

Personalized Medicine

The future of genomic testing in primary care: the changing face of personalized medicine

Primary care is recognized worldwide as a key component for improving health outcomes in the population. At the same time, healthcare systems are rapidly changing with increasing expectations from technological advances. Genomics is a major driver in changing how medicine is being practiced; however, the importance for primary care has been under-appreciated. Strategically implementing genomics in a way that accounts for the unique characteristics of the primary care context is essential. In this perspective, we present important areas that we believe are critical in consideration of both the future of genomic medicine and primary healthcare delivery.

Keywords: clinical decision support • cost–benefit analysis • genomics • personalized medicine • pharmacogenomics • primary care • public health

Gillian Bartlett*[,1], Vaso Rahimzadeh[1], Cristina Longo[1], Lori A Orlando[2], Martin Dawes[3], Jean Lachaine[4], Murielle Bochud[5], Fred Paccaud[5], Howard Bergman[1], Laura Crimi[1] & Amalia M Issa[6]

[1]Department of Family Medicine, McGill University, 5858 Cote-des-Neiges, Suite 300, Montreal, Quebec, H3S 1Z1, Canada

[2]Department of Medicine & Center for Personalized & Precision Medicine, Duke University, Wallace Clinic, Room 204, 3475 Erwin Rd, Duke Box 3022, Durham, NC 27705, USA

[3]Department of Family Practice, University of British Columbia, David Strangway Building Third floor, 5950 University Blvd, Vancouver, British Columbia, V6T 1Z3, Canada

[4]Faculté de Pharmacie, Université de Montréal, C.P. 6128, Succursale Centre-ville, Montréal, Québec, H3C 3J7, Canada

[5]University Institute of Social & Preventive Medicine, Lausanne University Hospital, Route de la Corniche 10, 1010 Lausanne, Switzerland

[6]Program in Personalized Medicine & Targeted Therapeutics & the Department of Health Policy & Public Health, University of the Sciences, 600 South 43rd Street, Philadelphia, PA 19104, USA

*Author for correspondence: gillian.bartlett@mcgill.ca

Personalized medicine in primary care

Primary care providers, including physicians, nurses and other healthcare professionals, are often the patient's first contact in the healthcare system. They serve as partners in managing chronic disease, gatekeepers to successive tiers in the healthcare system and act as health educators. Primary care acts as a critical intermediary between medicine and public health [1–3], bringing healthcare closest to where people live and work [4], and contextualizing patient needs against the sociocultural backdrop of the world in which they live [5,6]. This degree of personalization unique to primary care rests on an intimate understanding of a community's social and cultural fabric [7,8].

While primary care has been identified as a critical component for the delivery of high-quality healthcare and for the improvement of global health, we also live in the context of a rapidly changing healthcare system [9,10], with increasing expectations, knowledge and involvement of patients, families and communities [8,11]. There is a growing preoccupation with costs and performance leading to increased government intervention, control and reforms [12]. Finally, technological developments have created new hopes and expectations for primary care in what has become known as personalized medicine or personalized healthcare.

The concept of personalized medicine is very closely aligned with the ideas of patient-oriented care [7,8,13]. Personalized medicine has been defined in many ways, but one of the more accepted definitions has been provided by the National Human Genome Research Institute as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen" [14]. In other words, each person's unique clinical, genetic, genomic and environmental information influences the nature of diseases, their onset, their course and their response to medications in very individualized ways [15]. If personalized medicine cannot be integrated into primary care, there is a very real risk that genomic medicine will bankrupt healthcare systems with patients flooding tertiary care to

Future Medicine part of fsg

incorporate genomic information into disease prediction and treatment. This would also cause the issue of fragmentation of care to persist, as many individuals, particularly the elderly, have multiple chronic diseases and would potentially seek guidance from multiple specialists as to how best incorporate their genomic information into treatment strategies. An exploration of the benefits and challenges for integrating genomic medicine into primary care has begun in the scientific literature [16–19]. This includes the critical topic of education of primary care health professionals [20,21] on the topic of genomic medicine. From these initial efforts, we will explore in this perspective paper important issues that need to be considered for the strategic implementation of genomics into primary care, which we believe is critical for the future of both genomic medicine and primary healthcare delivery.

The fit of genomic medicine with whole-person primary care

Integrating genomics in a way that appreciates, and responds to, the complex ethical nuances of primary care practice necessitates a return to fundamental principles and central tenets of both health and healthcare. While many challenges guiding an ethically sound integration process are infrastructural, others require critical analysis of how genomic medicine must complement the central mandates of primary care, and specifically its commitment to whole-person care [22]. We propose that a strategic integration framework should center on the commonality between both genomic medicine and primary care: the capacity for personalization. Genomic profiling – and increasingly genomic literacy – augments patient empowerment through promoting a rich connection to one's genetic identity, while family medicine contextualizes healthcare in ways that appreciate the multidimensionality of patient health behaviors and wellbeing [23,24].

Personalization in the care setting can be achieved through a wide range of clinical activities across the genomic medicine and primary care continuum. Genomic applications have the potential capacity to evaluate drug efficacy, diagnose disease and provide information that can aid in making treatment recommendations, and the integration of genomic sequencing into primary care promises to facilitate health professionals in making more informed and improved decisions. Although there is potential for improved decision with the use of personalized medicine, there is still much that the scientific and healthcare communities do not know regarding genomic sequencing use and further investigation is required before widespread success can occur [25,26]. Whole-person care, alternatively, extends beyond genetic analysis, namely, assessing family history and creating platforms for shared decision-making and communication in accordance with patient beliefs and preferences. Together, this integration pushes the frontiers of disease diagnosis and prevention using genomic ingenuity.

The future of genomics in primary care is now: the role of pharmacogenomics

With technological advancements and scientific breakthroughs occurring in both pharmacogenomics and genomics, primary care is experiencing an unprecedented explosion of new knowledge, driven by the falling costs of DNA sequencing, which is outpacing clinical interpretation. In addition to pharmacogenomics, the use of genome-based companion diagnostics as diagnostic and predictive tools may lead to more judicious and appropriate use of therapies, including reducing adverse events, improving therapeutic outcomes and mitigating expenses. Pharmacogenomics, the study of the influence of genetic variation on individual differences in drug response, is one important component that is promising for applying genomics in primary care. Medication management is complex and fraught with potential harm for patients. An individual's response to drug therapy is affected by intrinsic factors (e.g., age, health and genetic variation) and extrinsic factors (e.g., diet, environment, concomitant drug use and adherence to therapy). For example, both clinical and demographic variables contribute to highly variable dose requirements for warfarin [27]. Genes relevant to the absorption, distribution, metabolism and excretion of a drug directly influence how an individual responds to that drug. Such variants include SNPs, copy number variations and other genetic variations caused by genomic insertions and deletions. A SNP is a DNA sequence variation where a single nucleotide – A, T, C or G – at a particular genomic location differs between individuals. SNPs can lead to protein function changes and/or protein expression levels that affect drug's absorption, distribution, metabolism and excretion, altering drug response. A copy number variation is a DNA segment that varies in copy number between individuals due to deletion, insertion, inversion, duplication or complex recombination. Copy number variations can lead to changes in protein expression levels (amounts) that affect drug's absorption, distribution, metabolism and excretion, thereby altering drug response.

In some cases, the outcome of an individual's genetic variation results in a reduced, or lack of, ability to metabolize a drug, leading to poor drug response that delays a positive treatment outcome for the patient. The current inability to predict those who will benefit or be harmed from a drug treatment

often leads to several drugs being tested on a patient before symptoms are reduced. This need to test drugs on a patient before finding 'the right combination' contributes to subsequent poor compliance, reduced effect and adverse drug reactions (ADRs), leading to poor outcomes for patients and significantly increased costs for the healthcare system [28]. Patients were two times more likely to be admitted to hospital if their emergency room visit was drug-related compared with patients with other medical problems and were more likely to make greater use of health services during a 6-month follow-up period [29]. Seniors are five times more likely to be hospitalized due to an ADR than the general population in Canada [29].

With over 65–75% of medications being prescribed in primary care [30,31], the field of pharmacogenomics provides a potential early win. The impact of gene variants can result in serious ADRs, leading to hospitalization, increased morbidity and mortality and significant costs to the healthcare system (~CAD$1 billion in British Columbia). With the advent of affordable high-throughput genotyping technologies, such as detection of SNPs and whole-genome sequencing, the influence of pharmacogenomics has evolved considerably. Genome-wide association studies (GWAS) have shown particular genomic variants to have a marked relationship with drug efficacy and ADR [32]. By targeting individuals and populations likely to be prescribed drugs that have such genetic profiles, pharmacogenomics has demonstrated the potential to improve the clinical effectiveness, decrease the numbers of ADR-related deaths and hospitalizations and reduce costs to the healthcare system [33]. While pharmacogenomics should not be considered a cure-all for the problem of adverse drug events, a recent review of a primary care setting found that one in four patients take at least one medication that commonly causes ADRs due to genetic variability in drug metabolism [34].

A number of international research institutions and consortia worldwide are undertaking and evaluating molecular and clinical pharmacogenomics research, including the NIH Pharmacogenomics Research Network and PharmGKB. PharmGKB is funded by the NIH and managed by Stanford University to produce a "pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene–drug associations and genotype–phenotype relationships" [35]. This resource rates levels of scientific and clinical evidence for each drug/SNP pair, details clinical annotations and cites relevant guidelines and publications. As pharmacogenomics research is evaluated, the US FDA updates a comprehensive list of pharmacogenomic biomarkers that are now added to drug labels [36]. There are now many gene–drug pairs that have been approved by the FDA as well as other regulatory bodies and pharmacogenomic information appears on the drug label of more than a hundred drugs, including several such as omeprazole, tramadol (acetaminophen) and warfarin, which are prescribed by primary care physicians [37]. These include many drugs used in primary care, such as warfarin, clopidogrel and common psychiatric drugs (e.g., selective serotonin reuptake inhibitors). As noted in a recent commentary, despite the potential benefits for individual patients being relatively small, given the large number of patients treated in primary care, even small benefits would result in a major population impact [37]. While there is single SNP test for individual drugs, this has not yet commonly been used in primary care practice. Clinical decision support is a key piece of the puzzle to promote implementation of genomics and pharmacogenomics in primary care [20,21,37].

The critical role of clinical decision support

There is growing interest in the implementation of clinical decision support systems that incorporate genetic variants and pharmacogenomic information into an electronic health record [38]. Clinical decision support has been defined as providing "clinicians, staff, patients or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and healthcare. It encompasses a variety of tools and interventions such as computerized alerts and reminders, clinical guidelines, order sets, patient data reports and dashboards, documentation templates, diagnostic support, and clinical workflow tools" [39]. It has been shown that in decision-making about genomic diagnostics, cancer patients place a high value on physician recommendations and interpretation of the results [40]. Physicians' adoption and use of pharmacogenomic and other genomic-based data have been proven to be dependent upon ease of use including interpretation of the genomic testing results [41]. Taken together, these findings suggest that any clinical decision support for personalized genomic medicine will need to have certain features in order to be successfully implemented in primary care practices.

One important characteristic of clinical decision support is point-of-care information, which would include a summary of the patient's active diagnoses, medications, labs, risk factors and such, as well as any pharmacogenomic label information relevant to the medications that the patient is on and for any medications indicated for the patient's diagnoses. This information on genetic variants and pharmacogenomics

should allow for a quick and easy means of interpretation of data, facilitating effective interpretation and development of recommendations for point-of-care decision-making. A second important feature is for the clinical decision support system to include a population registry that provides a mechanism for the continuous recording of selected information about each patient in the clinic. The registry can offer a more comprehensive view of the individual patient panel. Using specific diseases and markers, practices can identify patients with unmet needs and measure clinical performance, monitor adverse events and so on. It is critical for a clinical decision support system to function so as to enable personalized genomic medicine by acting in concert with the workflow of physicians and clinical practice.

A key area that would encourage the use of pharmacogenomics clinical decision support in primary care settings is pre-emptive clinical genotyping [14,42]. The goal of this approach is to genotype patients as part of routine preventative primary care, securely store their data and place the results in the patient record. Thus, when a particular drug is prescribed for a given patient, knowledge about and interpretation of the at-risk genotype for possible adverse events or drug responsiveness, with the relevant pharmacogenomic variability, will be made available along with possible treatment recommendations. Although this would certainly be a principal use of pharmacogenomics clinical decision support in primary care, there are logistical challenges, including an infrastructure for a coordinated biobanking, informatics and clinical decision support system. Without this infrastructure, any pre-emptive use of genotyping would remain limited to academic medical centers [14,42].

The economic impact of genomics: making the case for primary care

Economic considerations are also an important criterion for the implementation of genomics into routine primary care. The cost–effectiveness of a health intervention is based on its incremental cost and incremental effectiveness. Thus, when responders to a given treatment can be better identified, the effectiveness of this treatment will increase, and if the cost of treatment is unchanged, the incremental cost–effectiveness ratio will be more favorable. The potential favorable economic impact can be illustrated by the opportunity provided by pharmacogenomics to identify treatment responders or patients at risk of adverse events for certain medications: treating patients with a better chance to respond and avoiding futile or dangerous treatments. A positive economic impact would depend notably on the cost of the pharmacogenomic test, the number of subjects to be tested, the proportion of potential responders (or at risk of adverse events) in the targeted population and the cost of the treatment. For a condition for which a large number of subjects need to be tested, it could represent a significant cost even if the test is relatively inexpensive. On the other hand, if the biomarker of interest has a limited prevalence, the cost to identify a responder (or a subject at risk of adverse events) could be also substantial.

Another economic concern with pharmacogenomics-guided treatment is the cost of the treatment itself and the potential for market segmentation for drug manufacturers [43]. It is beneficial to limit the use of a treatment to the potential responders, but for a drug manufacturer, it limits the number of potential users. For example, suppose that a treatment for diabetes should be costed at CAD$1000 per year in order for the manufacturer to recuperate its investment and generate a reasonable profit. In the case that the same treatment could only be used in the 3% of the diabetic patients with the genetic trait of interest, the cost of the treatment could be as high as CAD$33,000 per year to be as profitable as if it was used for the larger diabetic population.

It is still early to conclude if pharmacogenomics-guided therapy will have a positive or negative overall economic impact in the long term. The segmentation of patients according to their genetic characteristics may lead to developing treatment for subsets of patients who will be in relatively low number [44]. An unfortunate scenario would be turning common chronic diseases with relatively affordable treatments into subgroups of rare diseases with the resulting high cost of personalized treatment. This may bring critical economic concerns, as it is being experienced with rare diseases. For this reason, the use of genomics in primary care will need to be strategic around economic concerns.

Using phenotype & family health history to enhance primary care

Although much of the focus has been on using the patient's genetic and genomic information to develop precise diagnostic tests and individualized therapies, personalized medicine also uses clinical and environmental information as well as family history of disease to tailor therapy. While we have examined the role of genomic testing in primary care, it is important to contrast this with patient characteristics that have a critical impact in primary healthcare delivery and may work synergistically with the use of genomic medicine. This is illustrated with the following two case studies: the issue of obesity and the role of the family health history (FHH).

Genomics & the obesity epidemic: optimizing primary care delivery

The obesity epidemic is a significant global health concern [45]. The 'globesity' problem presents a considerable burden on the primary healthcare system, since 60 and 26% of clinical patients are overweight and obese, respectively [46,47]. Visits to primary care physicians have also been reported to be approximately 38% higher for obese when compared with normal weight patients [48]. Primary care plays a pivotal role in the prevention, early detection, treatment and management of obesity and often serves as the first contact for weight-related comorbidities. Recent evidence from GWAS suggests shared genetic pathways for the development of obesity and other serious chronic illnesses such as cardiovascular disease, hypertension, diabetes, asthma and cancer among others [49–52]. To complicate matters, primary care physicians face the additional challenge of achieving therapeutic targets while treating these comorbid conditions in obese patients. Obese patients are more likely to exhibit blunted responses to medications and poorer clinical outcomes for rheumatoid arthritis [53], thrombotic disorders [54], asthma [55], pain [56] and depression [57] than their normal weight counterparts.

This type of weight-related treatment resistance is likely due to a combination of physiological and genetic factors. Excess fat leads to a variety of physiological changes, from hormone imbalances, immune system alterations and systemic inflammatory processes to direct modifications in blood flow and organ function, which ultimately affects medication disposition in the body and therapeutic effectiveness [58,59]. Fatty infiltration of the liver is common in obesity and this form of hepatitis, or liver damage in extreme cases, has been shown to influence the expression and activity levels of specific cytochrome P450 enzymes in humans, which may have significant prescribing implications for primary care physicians [60,61]. Investigating the relationship between obesity, drug pharmacokinetics and/or weight-associated genetic polymorphisms has recently become a new and important research avenue for clinical trials, some of which are currently underway [62–64].

Establishing personalized strategies for the management of acute and chronic diseases in the obese patient demographic is becoming more relevant, particularly as the field of pharmacogenomics continues to identify gene polymorphisms linked to both individuals who display the obese phenotype and those observed to have altered or suboptimal therapeutic responses to medications. This is critical in primary care to further clarify the relationship between obesity and poor clinical outcomes. While GWAS findings may currently be controversial, the rapid development of sequencing technology will eventually enable researchers to clarify disease-causing gene pathways that are also involved in the therapeutic response to drugs that treat these conditions. The integration and application of pharmacogenomics into primary care has the potential to improve risk assessment and could be an important aspect of optimizing treatment of obesity-related comorbidities.

Targeting genomics implementation with FHH

We have hypothesized that genomics could improve treatment of a complicated health issue such as obesity. Before genomics is even considered, however, the FHH remains one of the strongest predictors of an individual's disease risk [65,66]. In fact when looking at common complex diseases, it has significantly higher odds ratios than currently available SNP-based genomic tests; and when considering hereditary conditions, family history is the crucial element in determining whether an individual should undergo genetic testing or not. This is partly due to the limitations of SNP testing and partly due to the fact that FHH gives you more than just insight into genetics – it also provides insight into shared environments (e.g., homes where the parents smoke or there is lead-based paint). For these reasons, FHH collection and risk stratification is strongly endorsed by numerous preventive guidelines, including those for breast cancer, colon cancer, coronary artery disease and diabetes [67–70].

While primary care providers are peripherally aware of the benefits of collecting FHH and in theory broadly support its use, significant barriers exist; the end result is that few routinely collect and use FHH for preventive healthcare planning in their practice [71–76]. These barriers can be classified into three categories: limited time during a typical clinic visit to collect or discuss FHH, the poor quality of information gathered at the point of care and inability to synthesize FHH information into a clinically actionable healthcare plan [71–76]. Patients rarely are well enough informed about their family's history to be able to give an accurate history on the spot [72]. In addition, providers often fail to ask for enough information about each relative to be able to use it for risk stratification [73–76]. A high-quality FHH should include designation of lineage, gender, and relationship (i.e., maternal aunt or male paternal cousin), disease status and age of onset, age and cause of death if deceased, as well as any pertinent negatives in the family history [77]. Inability to synthesize data is a reflection of the complexity of the risk calculators and algorithms, and the failure to integrate them into tools readily available at the point of care.

One solution to some of these barriers is to leverage the burgeoning field of health information technology.

Health information technology is growing rapidly and is a perfect medium for the collection and synthesis of FHH. Although the collection of FHH can often be complex [25,78], health information technology could provide patient education about how to collect FHH from relatives and what to ask about, allow them to enter their data into a web or portal base software program prior to their clinic appointment and run the complex calculations and algorithms needed to give providers straightforward action-oriented recommendations tailored to a patient's risk level. This model has been successfully used by MeTree, Family Healthware [79] and Health Heritage [80], and in a modified form by Hughes Risk Apps (providers must enter the data) [81]. When using these tools, between 42 and 82% of the general population was found to be at an increased risk for at least one condition depending upon the number of conditions being evaluated and the criteria for assigning risk [80,82,83], representing a substantial portion of the population who would benefit from risk assessment and targeted risk management strategies. Realizing this model would fulfill the public health goal of right patient, right care, right time for preventive healthcare.

As we have begun to successfully develop models for integrating FFH into primary care clinical practice, the next step will be to merge the information reflected in genomic testing with that from FHHs. Currently, there are no large studies that compare and contrast the information provided by genomic tests and FHH, but small studies suggest that there is also synergy and complementary information between these two [84]. If larger studies prove this to be true, we may be able to use FHH to target genomic testing to those most likely to benefit from it then include both FHH and genomic testing within a risk prediction calculation. Or, as large-scale sequencing gets underway, we may find that the information is complementary and that everyone should undergo both [85]. The models developed to integrate FHH into the primary care settings can then be adapted to accommodate genomic/genetic data into the risk assessment algorithms.

Genomic medicine at the crossroads of primary care & public health

The genomic revolution touches the domains of transcriptomics (i.e., the study of genome-wide gene expression), metabolomics (i.e., the study of metabolites in a specific medium), proteomics (i.e., the study of the entire set of proteins in a specific medium, such as a cell type) and epigenomics (i.e., the study of DNA methylation patterns and/or histone modifications susceptible to influence gene expression). Novel high-throughput laboratory techniques generate massive data that come with specific challenges in terms of storage, cleaning, analysis as well as translation. Overcoming the logistical issues of 'big data' combined with the increasing affordability of whole-genome sequencing, will eventually translate into useful applications at for primary care and public health.

So far, more than 2000 GWAS have been published covering a wide range of phenotypes, including common chronic diseases [86]. After unrealistic high expectations following the completion of the first human genome sequencing in 2000, applications that have clinical and population impact have been slow to materialize. As noted previously, selected areas such as pharmacogenomics, have already started to produce useful tests that could be incorporated in primary care. As nicely summarized by Manolio [86], clinically useful GWAS findings have occurred in four main areas: prediction of diseases (e.g., Type 1 diabetes, age-related macular degeneration) and risk reclassification; disease classification (e.g., breast cancer); drug development; and drug toxicity (e.g., statin-induced myopathy and *SLCO1B1* variants) [87]. Undoubtedly, the main current contribution of GWAS findings is a better understanding of disease biology.

An example of an area of interest for future development in public health genomics closely related to the primary care mandate is nutrigenomics and nutrigenetics. This field takes genomic variation into account when exploring the effect of diet on human health. It encompasses but is not limited to the following questions: does a specific nutrient similarly impact on health across different genetic backgrounds? Do genetic factors influence the way we eat (e.g., by influencing our ability to taste and smell selected substances)? How does diet influence gene expression? Can genetic information be used to target public health screening? Can knowledge of genetic risk motivate behavior change? Answers to these questions are currently fragmentary, but will be key for the crossroads of primary care, public health and genomic testing.

Conclusion

Primary care is often seen as the 'gatekeeper' for patient-centered care. Personalized medicine has not yet made inroads into primary care, but as we demonstrate in this article, it should be, and it is critically important to strategically incorporate genomics into primary care. Doing so promises benefits for primary care and health systems.

Future perspective

Translating findings from genomics, pharmacogenomics and related -omics fields into clinical applications capable of reducing the burden of chronic diseases,

remains an enormous challenge [88]. We propose a strategic integration framework that includes the following elements: ensuring the fit of genomic medicine with the key approach of whole-person care through personalization; targeting areas that will see early benefit such as pharmacogenomics; ensuring that appropriate clinical decision support is available that supplements any education efforts for primary care providers; assessing the economic impact of genomic medicine to determine optimal implementation; supplementing genomic information with patient information including the full FHH; and looking to the future for areas of development such as the intersection of public health, primary care and genomics. Our strategic framework builds on early work that emphasizes the role of education and step-wise implementation [18,20,21,89]. Effective ways to continuously review and summarize the rapidly accumulating complex knowledge are needed to facilitate policy decisions and evidence-based recommendations [88]. As stated by Khoury *et al.*, "implementation

Executive summary

Personalized medicine in primary care

- Primary care providers are often the patients' first contact in the healthcare system.
- If personalized medicine cannot be integrated into primary care, there is a very real risk that genomic medicine will bankrupt healthcare systems with patients flooding tertiary care to incorporate genomic information into disease prediction and treatment.
- We explore important issues that need to be considered for the strategic implementation of genomics into primary care that we believe are critical for the future of both genomic medicine and primary healthcare delivery.

The fit of genomic medicine with whole-person primary care

- A strategic integration framework should center on the commonality between both genomic medicine and primary care: the capacity for personalization.

The future of genomics in primary care is now: the role of pharmacogenomics

- Pharmacogenomics, the study of the influence of genetic variation on individual differences in drug response, is one important component that is promising for applying genomics in primary care.
- There are now many gene–drug pairs that have been approved by regulatory bodies including several such as omeprazole, tramadol (acetaminophen) and warfarin that are prescribed by primary care physicians.
- With over 65–75% of medications being prescribed in primary care, the field of pharmacogenomics provides a potential early win.

The critical role of clinical decision support

- There is growing interest in the implementation of clinical decision support systems that incorporate genetic variants and pharmacogenomic information into an electronic health record.
- A key area that would encourage the use of pharmacogenomics clinical decision support in primary care settings is pre-emptive clinical genotyping.
- Clinical decision support needs to provide point-of-care information including a summary of the patient's active diagnoses, medications, labs, risk factors and such, as well as any pharmacogenomic label information relevant to the medications that the patient is on and for any medications indicated for the patient's diagnoses.

The economic impact of genomics – making the case for primary care

- Economic considerations are an important criterion for the implementation of genomics into routine primary care.
- A positive economic impact would depend notably on the cost of the pharmacogenomic test, the proportion of potential responders in the targeted population and the cost of the treatment.
- On the other hand, another economic concern with pharmacogenomics-guided treatment is the potential for market segmentation for drug manufacturers.

Using phenotype & family health history to enhance primary care

- In addition to the use of genomics to develop diagnostic and prognostic tools for treatment recommendations in primary care, there are complimentary effort such as the use of family health history and clinical phenotype that can improve health outcome in primary care.

Genomic medicine at the crossroads of primary care & public health

- Genomics includes transcriptomics, metabolomics, proteomics, nutrigenomics and epigenomics – all areas that overlap between public health and primary care.

Future perspective

- When we can provide personalized medicine interventions that are more cost-effective than population-based measures, we will have guaranteed the future place of genomics in primary care.

science, health services, outcomes research, comparative effectiveness research, and regulatory science are needed for moving validated genomic applications into practice and for measuring their effectiveness, cost–effectiveness, and unintended consequences" [88]. Whereas population-based measures will remain the cornerstone in the fight against chronic diseases, more personalized approaches that account for genomics as well as other patient characteristics such as obesity, ethnicity, FHH and drug efficacy, tolerance and toxicity need to be included in order to more effectively provide more holistic integrated primary care. When we can provide personalized medicine interventions that are more cost effective than population-based measures, we will have guaranteed the future place of genomics in primary care.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Canadian Foundation for Healthcare Improvement. Strengthening primary health care through primary care and public health collaboration. www.cfhi-fcass.ca/SearchResultsNews/12-12-14/5a626084-a6e6-4c75-a421-feb115ccead5.aspx

2 Linde-Feucht S, Coulouris N. Integrating primary care and public health: a strategic priority. *Am. J. Prev. Med.* 42(6), S95–S96 (2012).

3 Institute of Medicine Committee on Integrating Primary Care. Primary care and public health: exploring integration to improve population health. http://books.nap.edu/openbook.php?record_id=13381

4 Canadian Pharmacists Association: Interdisciplinary collaboration in primary health care. *Can. Pharm. J. (Ott.)* 140, S5–S7 (2007).

5 Vanderford ML, Jenks EB, Sharf BF. Exploring patients' experiences as a primary source of meaning. *Health Commun.* 9(1), 13–26 (1997).

6 Scholle SH, Weisman CS, Anderson R, Weitz T, Freund KM, Binko J. Women's satisfaction with primary care: a new measurement effort from the PHS National Centers of Excellence in Women's Health. *Womens Health Issues* 10(1), 1–9 (2000).

7 Starfield B. Is primary care essential? *Lancet* 344(8930), 1129–1133 (1994).

8 Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. *Milbank Q.* 83(3), 457–502 (2005).

9 Frenk J. Dimensions of health system reform. *Health Policy* 27(1), 19–34 (1994).

10 Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. *Trans. R. Soc. Trop. Med. Hyg.* 100(3), 191–199 (2006).

11 Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. *Health Aff.* 20(6), 64–78 (2001).

12 Smith M, Saunders R, Stuckhardt L, McGinnis JM. *Best Care at Lower Cost: the Path to Continuously Learning Health Care in America.* National Academies Press, Washington, DC, USA (2013).

13 Kaelber DC, Jha AK, Johnston D, Middleton B, Bates DW. A research agenda for personal health records (PHRs). *J. Am. Med. Inform. Assoc.* 15(6), 729–736 (2008).

14 Pulley JM, Denny JC, Peterson JF *et al.* Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin. Pharmacol. Ther.* 92(1), 87–95 (2012).

15 Hamburg MA, Collins FS. The path to personalized medicine. *N. Engl. J. Med.* 363(4), 301–304 (2010).

16 Leitsalu L, Hercher L, Metspalu A. Giving and withholding of information following genomic screening: challenges identified in a study of primary care physicians in Estonia. *J. Genet. Couns.* 21(4), 591–604 (2012).

17 Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. *JAMA Intern. Med.* 174(2), 275–280 (2013).

18 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.* 9(10), 665–674 (2007).

•• **Framework for the implementation of genomic medicine.**

19 Emery J, Watson E, Rose P, Andermann A. A systematic review of the literature exploring the role of primary care in genetic services. *Fam. Pract.* 16(4), 426–445 (1999).

20 Houwink EJF, Van Luijk SJ, Henneman L, Van Der Vleuten C, Dinant GJ, Cornel MC. Genetic educational needs and the role of genetics in primary care: a focus group study with multiple perspectives. *BMC Fam. Pract.* 12(1), 5 (2011).

• **Exploration of the educational needs around implementing genomics in primary care.**

21 Carroll JC, Rideout AL, Wilson BJ *et al.* Genetic education for primary care providers: improving attitudes, knowledge, and confidence. *Can. Fam. Physician* 55(12), e92–e99 (2009).

• **Proposal for methods to educate primary care providers about genomic medicine.**

22 Bartlett G, Antoun J, Zgheib NK. Theranostics in primary care: pharmacogenomics tests and beyond. *Expert Rev. Mol. Diagn.* 12(8), 841–855 (2012).

23 Tubesing DA. *Wholistic health: a Whole-Person Approach to Primary Health Care.* Human Sciences Press, NY, USA (1979).

24 Hutchinson TA. *Whole Person Care: a New Paradigm for the 21st Century.* Springer, NY, USA (2011).

25 Feero WG. Clinical application of whole-genome sequencing: proceed with care. *JAMA* 311(10), 1017–1019 (2014).

26 Dewey FE, Grove ME, Pan C *et al.* Clinical interpretation and implications of whole-genome sequencing. *JAMA* 311(10), 1035–1045 (2014).

27 International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB *et al.* Estimation of the warfarin dose with clinical and pharmacogenetic data. *N. Engl. J. Med.* 360(8), 753–764 (2009).

28 Hajjar ER, Hanlon JT, Artz MB *et al.* Adverse drug reaction risk factors in older outpatients. *Am. J. Geriatr. Pharmacother.* 1(2), 82–89 (2003).

29 Canadian Institute for Health Information. Adverse drug reaction-related hospitalizations among seniors, 2006–2011. https://secure.cihi.ca/estore/productFamily.htm?pf=PFC2128&lang=en

30 Soumerai SB, Mclaughlin TJ, Avorn J. Improving drug prescribing in primary care: a critical analysis of the experimental literature. www.ncbi.nlm.nih.gov/pmc/articles/PMC2690287

31 De Bakker DH, Coffie DS, Heerdink ER, Van Dijk L, Groenewegen PP. Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. *BMC Health Serv. Res.* 7(1), 132 (2007).

32 Harper A, Topol E. Pharmacogenomics in clinical practice and drug development. *Nat. Biotechnol.* 30(11), 1117–1124 (2012).

33 Vegter S, Jansen E, Postma MJ, Boersma C. Economic evaluations of pharmacogenetic and genomic screening programs: update of the literature. *Drug Dev. Res.* 71(8), 492–501 (2010).

34 Grice GR, Seaton TL, Woodland AM, Mcleod HL. Defining the opportunity for pharmacogenetic intervention in primary care. *Pharmacogenomics* 7(1), 61–65 (2006).

35 The Pharmacogenomics Knowledgebase. www.pharmgkb.org/aboutUs.jsp

36 US FDA. Drugs: Table of pharmacogenomic biomarkers in drug labeling. www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

37 Swen JJ, Guchelaar HJ. Just how feasible is pharmacogenetic testing in the primary healthcare setting? *Pharmacogenomics* 13(5), 507–509 (2012).

38 Overby Cl, Kohane I, Kannry JL *et al.* Opportunities for genomic clinical decision support interventions. *Genet. Med.* 15(10), 817–823 (2013).

39 Osheroff J, Teich JM, Middleton B, Steen EB, Wright A, Detmer DE. A roadmap for national action on clinical decision support. *J. Am. Med. Inform. Assoc.* 14(2), 141–145 (2007).

40 Issa AM, Tufail W, Atehortua N, McKeever J. A national study of breast and colorectal cancer patients' decision-making for novel personalized medicine genomic diagnostics. *Per. Med.* 10(3), 245–256 (2013).

41 Issa AM, Patil D. Factors affecting the adoption and use of gene expression profiling by oncologists in clinical practice. Presented at: *35th Annual Meeting of the Society for Medical Decision Making.* Baltimore, MD, USA, 23 October 2013.

42 O'Donnell P, Bush A, Spitz J *et al.* The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. *Clin. Pharmacol. Ther.* 92(4), 446–449 (2012).

43 Wedlund P, De Leon J. Pharmacogenomic testing: the cost factor. *Pharmacogenomics J.* 1(3), 171–174 (2001).

44 Issa AM. Ethical perspectives on pharmacogenomic profiling in the drug development process. *Nat. Rev. Drug Discov.* 1(4), 300–308 (2002).

45 WHO: Obesity and overweight. www.who.int/mediacenter/factsheets/fs311/en

46 Tjepkema M, Sheilds M. *Measured Obesity.* Health Statistics Division, Statistics Canada, Ottawa, Canada (2005).

47 Mongeau L, Audet N, Aubin J, Bararldi R. [The excess weight in the Quebec population from 1987 to 2003]. www.bdso.gouv.qc.ca/docs-ken/multimedia/PB01670FR_poids_qc1987_2003_2005H00F00.pdf

48 Wilborn C, Beckham J, Campbell B *et al.* Obesity: prevalence, theories, medical consequences, management, and research directions. *J. Int. Soc. Sports Nutr.* 2, 4–31 (2005).

49 Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu. Rev. Med.* 61, 301–316 (2010).

50 Melen E, Himes BE, Brehm JM *et al.* Analyses of shared genetic factors between asthma and obesity in children. *J. Allergy Clin. Immunol.* 126(3), 631–637 (2010).

51 Jafar-Mohammadi B, McCarthy MI. Genetics of Type 2 diabetes mellitus and obesity – a review. *Ann. Med.* 40(1), 2–10 (2008).

52 Pausova Z, Deslauriers B, Gaudet D *et al.* Role of tumor necrosis factor-alpha gene locus in obesity and obesity-associated hypertension in French Canadians. *Hypertension* 36(1), 14–19 (2000).

53 Kaasen R, Wijbrandts CA, Gerlag DM, Tak PP. Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis Rheum.* 63, 359–364 (2011).

54 Badimon L, Hernandez Vera R, Padro T, Vilahur G. Antithrombotic therapy in obesity. *Thromb. Haemost.* 110(4), 681–688 (2013).

55 Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? *Ann. Allegery Asthma Immunol.* 108(4), 237–242 (2012).

56 Lloret-Linares C, Lopes A, Decleves X *et al.* Challenges in the optimisation of post-operative pain management with opioids in obese patients: a literature review. *Obes. Surg.* 23(9), 1458–1475 (2013).

57 Kloiber S, Ising M, Reppermund S *et al.* Overweight and obesity affect treatment response in major depression. *Biol. Psychiatry* 62(4), 321–326 (2007).

58 Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin. Pharmacokinet.* 39(3), 215–231 (2000).

59 Shore SA, Johnston RA. Obesity and asthma. *Pharmacol. Ther.* 110(1), 83–102 (2006).

60 Morrish GA, Pai MP, Green B. The effects of obesity on drug pharmacokinetics in humans. *Expert Opin. Drug Metab. Toxicol.* 7(6), 697–706 (2011).

61 Cho SJ, Yoon IS, Kim DD. Obesity-related physiological changes and their pharmacokinetic consequences. *J. Pharm. Invest.* 43(3), 161–169 (2013).

62 St Antonius Hospital. Pharmacokinetics of acetaminophen in morbidly obese patients (APAP). www.trialdetails.com/detail/NCT01764555/Pharmacokinetics-of-Acetaminophen-in-Morbidly-Obese-Patients

63 Children's Mercy Hospital Kansas City. Pharmacokinetics of pantoprazole and CYP2C19 activity in children and adolescents with GERD: a pilot study. http://clinicaltrials.gov/show/NCT01887743

64 Ghose R. Clinical consequences of altered drug disposition in obesity. *J. Clin. Trials* 1, e107 (2012).

65 Meigs JB, Shrader P, Sullivan LM *et al.* Genotype score in addition to common risk factors for prediction of Type 2 diabetes. *N. Engl. J. Med.* 359(21), 2208–2219 (2008).

66 Easton DF, Eeles RA. Genome-wide association studies in cancer. *Hum. Mol. Genet.* 17(R2), R109–R115 (2008).

67 Greenland P, Alpert JS, Beller GA *et al.* 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 122(25), 2748–2764 (2010).

68 American Diabetes A. Standards of medical care in diabetes – 2011. *Diabetes Care* 34(Suppl. 1), S11–S61 (2011).

69 Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J. Clin.* 59(1), 27–41 (2009).

70 Levin B, Lieberman DA, Mcfarland B *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J. Clin.* 58(3), 130–160 (2008).

71 Audrain-Mcgovern J HCPF: effecting behavior change: awareness of family history. *Am. J. Prev. Med.* 24(2), 183–189 (2003).

72 Qureshi N, Wilson B, Santaguida P *et al.* Collection and use of cancer family history in primary care. *Evid. Rep. Technol. Assess. (Full Rep).* 159, 1–84 (2007).

73 Gramling R, Nash J, Siren K, Eaton C, Culpepper L. Family physician self-efficacy with screening for inherited cancer risk. *Ann. Fam. Med.* 2(2), 130–132 (2004).

74 Barrison AF, Smith C, Oviedo J, Heeren T, Schroy PC 3rd. Colorectal cancer screening and familial risk: a survey of internal medicine residents' knowledge and practice patterns. *Am. J. Gastroenterol.* 98(6), 1410–1416 (2003).

75 Acton RT, Burst NM, Casebeer L *et al.* Knowledge, attitudes, and behaviors of Alabama's primary care physicians regarding cancer genetics. *Acad. Med.* 75(8), 850–852 (2000).

76 Berg AO, Baird MA, Botkin JR *et al.* National Institutes of Health State-of-the-Science Conference statement: Family history and improving health. *Ann. Intern. Med.* 151(12), 872–877 (2009).

77 Powell KP, Christianson CA, Hahn SE *et al.* Collection of family health history for assessment of chronic disease risk in primary care. *N. C. Med. J.* 74(4), 279–286 (2013).

78 Baer HJ, Schneider LI, Colditz GA *et al.* Use of a web-based risk appraisal tool for assessing family history and lifestyle factors in primary care. *J. Gen. Intern. Med.* 28(6), 817–824 (2013).

79 Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. *Prev. Chronic Dis.* 6(1), A33 (2009).

80 Cohn W, Ropka M, Pelletier S *et al.* Health Heritage©, a web-based tool for the collection and assessment of family health history: initial user experience and analytic validity. *Public Health Genomics* 13(7–8), 477–491 (2010).

81 Ozanne EM, Loberg A, Hughes S *et al.* Identification and management of women at high risk for hereditary breast/ovarian cancer syndrome. *Breast J.* 15(2), 155–162 (2009).

82 O'Neill SM, Rubinstein WS, Wang C *et al.* Familial risk for common diseases in primary care: the Family Healthware Impact Trial. *Am. J. Prev. Med.* 36(6), 506–514 (2009).

83 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.* 13(11), 956–965 (2011).

84 Mealiffe ME, Stokowski RP, Rhees BK *et al.* Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. *J. Natl Cancer Inst.* 102(21), 1618–1627 (2010).

85 Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. *Genet. Med.* 11(8), 570–574 (2009).

86 Manolio TA. Bringing genome-wide association findings into clinical use. *Nat. Rev. Genet.* 14(8), 549–558 (2013).

87 Link E, Parish S, Armitage J *et al.* SLCO1B1 variants and statin-induced myopathy – a genomewide study. *N. Engl. J. Med.* 359(8), 789–799 (2008).

88 Khoury MJ, Clauser SB, Freedman AN *et al.* Population sciences, translational research, and the opportunities and challenges for genomics to reduce the burden of cancer in the 21st century. *Cancer Epidemiol. Biomarkers Prev.* 20(10), 2105–2114 (2011).

89 Houwink EJF, Sollie AW, Numans ME, Cornel MC. Proposed roadmap to stepwise integration of genetics in family medicine and clinical research. *Clin. Transl. Med.* 2(1), 1–5 (2013).

•• **Proposed framework for integration of genomic medicine into primary care.**