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Chapter 3

THE PRECISION MEDICINE AND PRECISION PUBLIC HEALTH APPROACHES TO CANCER TREATMENT AND PREVENTION: A CROSS-COMPARISON

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ABSTRACT

Like other forms of diagnostics, genetic testing comes with a retinue of costs and benefits. Significant benefits in terms of morbidity and mortality have accrued to individuals tested for more prevalent genetic

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conditions like cystic fibrosis and sickle cell disease, including persons seen in the emergency room or identified through public health surveillance. These benefits do not mitigate the drawbacks of genetic testing, false and missed diagnoses and sheer cost among them.

Both medicine and public health have aimed at means of maximizing genetic test benefits in the interventions that they apply. The President's Precision Medicine Initiative (PMI) holds promise in that its results could be used to tailor medical treatments to the individual characteristics of patients, "precision" implying a more accurate and precise regimen overall. The National Cancer Institute (NCI) has already launched the NCI-MATCH precision medicine trial, which assigns targeted treatments based on the genetic abnormalities in a tumor, regardless of cancer type. Other trials, such as the NCI Pediatric MATCH trial, are yet to happen. The efficacy of cancer treatments also intersects public health concerns. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has evaluated the use of *UGT1A1* genotyping to determine the best dose of irinotecan to prevent side effects when treating patients for metastatic colorectal cancer. Analytic validity does not always equate with improved patient outcomes, however, thus the public health emphasis on development of a suitable evidence base for precision medical and public health efforts.

The public health approach to precision medicine, or "precision public health", differs from the medical approach in several important ways: (1) population-based with attention to at-risk populations, as opposed to being strictly individualized; (2) focus on primary and secondary prevention, rather than frank disease (tertiary prevention); and (3) prioritizing interventions that have already demonstrated readiness for large-scale implementation, in contrast to the undertaking of novel clinical trials. Precision public health is exemplified in the Centers for Disease Control and Prevention's emphasis on the implementation of Tier 1 genetic tests that have passed systematic review for analytic and clinical validity and utility – the use of family history for referral for hereditary breast and ovarian cancer genetic testing (*BRCA1/2* mutations), and hereditary nonpolyposis colorectal cancer cascade screening (Lynch syndrome *MLH1*, *MSH2*, *MSH6* mutations).

This paper will cross-compare the precision medical approach to cancer based on pharmacogenomic regimens using companion diagnostics, and the public health approach to precision management of hereditary cancer for 3 cancer types – lung, breast, and colorectal. It will describe methods of early detection and consider how lives can be saved through precise management – from predictive testing and cancer monitoring of the at-risk population, to tailored chemoprevention that fits the needs of the individual. In the population context, a cascade screening "multiplier effect" exists in that relatives can also be assessed and followed for mutations identified in the proband. Cost-benefit analyses

(T4 translational research) of medical and public health approaches will be closely examined and compared. Points of commonality between the two approaches will also be discussed, since primary/secondary and tertiary disease prevention represent a continuum. These analyses point to the value of allocating resources towards the health of at-risk populations. Questions remain if particular forms of genetic testing are to become "universalized", and if the needs of all at-risk groups, including racial-ethnic, are to be addressed.

Keywords: lung cancer, breast cancer, colorectal cancer, Lynch syndrome, genetic testing, cascade screening, universal screening, cost-effectiveness, precision medicine, pharmacogenomics, public health, race, ethnicity

FROM THE HUMAN GENOME PROJECT TO THE PRECISION MEDICINE INITIATIVE

If the twentieth century is known for its success in mapping the human genome, the twenty-first century is becoming equally well known for scientists' attempts at making genetic interventions "precise" – appropriately chosen, and delivered to the right person and physical target within the human body. The Precision Medicine Initiative (PMI), launched by the Obama administration in January 2015 with a $215 million outlay in the President's 2016 Budget and continuing onward in the current administration, brought medicine closer than ever to the ability to tailor medical regimens to the needs of the individual patient [1]. An article by Francis Collins, Director of the U.S. National Institutes of Health (NIH), and Harold Varmus, former Director of the U.S. National Cancer Institute (NCI), which appeared shortly after the announcement, broke the Initiative into two stages: a near-term focus on cancers, and a longer-term aim to yield new knowledge applicable to the broader range of health and disease [2]. Muin Khoury, Director of the Office of Public Health Genomics at the U.S. Centers for Disease Control and Prevention (CDC-OPHG), and Sandro Galea, Dean of Boston University School of Public Health, followed-up with the affirmation that the PMI could, in time, be used to develop, evaluate, and deliver health interventions with greater "precision" for both individuals and populations [3].

The distance between a strictly individualized approach to precision medicine and one that is population-oriented, fitting the right intervention to the right population, is transcended by a common denominator shared by

medicine and public health – cost-effectiveness. Translational research spans several distinct territories, from basic genome-based discovery as it yields candidate health applications (e.g., new genetic tests and therapeutic interventions) - T1 translational research, to evaluation of real-world outcomes (e.g., morbidity and mortality, cost-effectiveness, and quality-of-life indicators) - T4 translational research [4]. In this piece we take the position that whatever the molecular genetic or behavioral approach used, it must make sense dollar-wise such that the interventions are being mustered in an effective and economical way. Our analysis will show that the criterion of cost-effectiveness naturally shifts the prospect of a national precision medicine effort in the population-oriented direction. Though the two may seem like strange bedfellows, both the pharmacogenomics industry and public health community are in agreement that the PMI must be a sustainable effort, so that the real question becomes, "What direction(s) can the PMI effectively take?".

DEFINITIONS OF PRECISION MEDICINE AND PRECISION PUBLIC HEALTH

The definition of a particular medical intervention illustrates both the basic actions to be taken and its scope. Jameson and Longo define "precision medicine" as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" [5]. Implicit in this definition is the goal of improving clinical outcomes for individual patients, while avoiding unnecessary side-effects that could be incurred by ignoring patients' individual characteristics. The authors admit that medicine to date has more or less employed such an approach. Hemophilia requires the administration of an appropriate clotting factor, be it factor VIII or factor IX (these days in recombinant form), to stop the bleeding. Clinicians need to undertake a thorough work-up in order to arrive at a precise diagnosis of the hemophilia, which will enable the appropriate therapy to be administered. Choice of antibiotic is another example. For the antibiotic to take hold, the right type of antibiotic must be given for the particular bacterial infection. The latter example suggests that targeted approaches, aimed at particular persons for specific conditions, could actually have population-level applicability, since antibiotics and vaccinations are given on a widespread

basis. They are the very opposite of "orphan drugs", designed to cater to the needs of very rare cases.

Shen and Hwang point out that despite the commonality with past precedent, a substantive shift in methodology between the old medicine and the new medicine is occurring [6]. The practice of medicine has so far remained largely "empirical". Physicians typically rely on a combination of patient and occasionally family medical history, physical examination, and laboratory data to secure a diagnosis and choose a drug. Treatments are based on a provider's experience with similar patients. Drugs administered are most often "blockbuster" drugs designed to accommodate the "typical" patient. If the wrong analgesic, antibiotic, or antiarrhythmic is given, the patient will be weaned off the current drug, and a new one tested until the right drug and dosage are chosen. The idea behind precision medicine is to rely on new biomarkers and genomic tests to "deliver the right treatment to the right patient at the right time" [6]. It is a personally tailored, as opposed to "one size fits all" approach. The fit is "precise" – one person; one drug.

Classic pharmacogenomic examples readily demonstrate this novel approach. Warfarin (brand name Coumadin) dosing allows the frequently used anticoagulant to be titrated to the needs of the patient susceptible to clotting events associated with atrial fibrillation and deep vein thrombosis [7]. Two genes are known to be involved in warfarin therapeutic outcomes – *CYP2C9*, which codes for an enzyme primarily responsible for warfarin metabolism, and *VKORC1*, which codes for the warfarin drug target. Genotyping can yield information useful to guide a person's initial warfarin dose and allow the clinician to readily stabilize his or her prothrombin measures, a process which usually takes several weeks. Cost-effectiveness studies of genotype-guided dosing have concluded that considerable potential exists for cost savings, but that it cannot be realized until test costs decrease and the uncertainty concerning effectiveness is reduced. The U.S. Centers for Medicare and Medicaid Services (CMS) has consequently adopted a provisional "coverage with evidence development" approach [7]. A physiologic measure, the ratio of the patient's prothrombin time to a control or "normal" sample, continues to be the professional standard for warfarin dosing. Since the patient is followed with this measure, its use may be considered a tool in "personalized" or individually-tailored medicine.

Imatinib (Gleevec) for chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors is another prime example of the tailoring in drug regimens that may take place. Medical researchers developed this drug over a multi-decade period to inhibit the function of a translocation-related

"fusion" gene, *BCR-Abl*, which produces an abnormal tyrosine kinase that is not properly regulated [8]. In initial trials, all of 31 research participants experienced complete remission. The five year survival rate for CML has increased from 31% (1993) to 59% (2003 – 2009) [9]. The drug is administered to patients who are Ph+ (Philadelphia chromosome positive), with effectiveness monitored by white blood cell and platelet counts. Like warfarin, Gleevec targets a particular type of patient and has a very specific chemical target – the ATP-binding site on a particular kinase – and is a drug that can be closely monitored. Gleevec's cost is about $3,500 per month, which may evade some patients' pocketbooks. However, it is covered by Medicare Part D and Medicare Advantage Plans. Both of the above examples describe "personalized medicine" – separating patients into different groups then individually tailoring the treatment to the patient.

Though many authors use the two terms interchangeably, Khoury distinguishes "personalized medicine" from "precision medicine" in that the latter inculcates multiple determinants of health, genetics being one rung, thus can absorb the notion of social determinants as easily as it can molecular determinants. The President's PMI plan is data intensive in a way that would allow the recording of multiple determinants for large numbers of people, ostensibly through a planned million-person cohort:

> Participants will be involved in the design of the Initiative and will have the opportunity to contribute diverse sources of data – including medical records; profiles of the patient's genes, metabolites (chemical makeup), and microorganisms in and on the body; environmental and lifestyle data; patient generated information; and personal device and sensor data. [1]

Collins and Varmus write that the numerous clinical trials stemming from the PMI and its large-scale cohort will require the building of a "cancer knowledge network" to store all the resulting molecular and medical data in digital form and make it readily deliverable to providers and patients [2]. Simonds and Khoury illustrate this idea with the example of a cancer clinical trials and effectiveness research infrastructure developed by the H. Lee Moffitt Cancer Center. The system is part of its personalized cancer care initiative started in 2006 – Total Cancer Care. The program: (1) integrates data from multiple sources (electronic medical records, biospecimen databases, and molecular data); (2) makes resultant information available to patients by providing active feedback about their health and upcoming appointments and

expanded electronic health record; and (3) affords data interfaces for researchers and clinicians [10].

It is to be hoped that the streamlining of cancer clinical trials and centralization of incoming data will reduce costs and increase efficiency over standard medical practices. According to Cancer Research U.K., between 2003 and 2007 cancer trials were accompanied by a 75% increase in administrative costs, a figure in need of remedy [11]. Cost-effectiveness and clinical utility will enter into assessments of the PMI. Public health efforts in the U.S. have to date assumed a twin duty – assessment of the cost-effectiveness of clinical programs, at the same time that a vision of precision medicine's meaning in terms of population health is being formulated. This vision departs from the medical model of precision health in a number of important respects: (1) it is population-based, with attention to at-risk populations, as opposed to being strictly individualized; (2) the focus is on primary and secondary prevention, rather than frank disease (tertiary prevention); and (3) the emphasis is on interventions that have already demonstrated readiness for large-scale implementation, in contrast to the undertaking of novel clinical trials [12]. To glimpse the future, it is helpful to visit recent experience with precision medicine in the cancer arena. This inspection will take our trek from the individually-focused domain of clinical medicine to the population-oriented territory of public health. The next section will focus on three major cancer categories of mutual interest to clinical medicine and public health – lung, breast, and colorectal cancer – from the medical pharmacogenomics point of view.

PHARMACOGENOMIC INTERVENTIONS AND COST-EFFECTIVENESS

The Precision Medicine Approach to Lung Cancer

Lung cancer is the second most common cancer in both men and women, and is the leading cause of cancer-related death in both genders [13, 14]. Of note, the lung cancer incidence rate for black women is roughly equal to that of white women, despite the fact that they smoke fewer cigarettes [13]. The two major forms of lung cancer are non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). NSLC comprises ~85% of all lung cancers;

SCLC ~10-15% [15]. The 5-year survival rate for NSCLC is 21%, suggesting progress that has been and that is yet to be made [16].

Targeted therapies aimed at cancers harboring very specific genetic alterations are becoming more and more common in oncogenomics. A 2012 review of the role of pharmacogenomics in moving genetic association studies from bench to bedside describes the use of EGFR tyrosine kinase inhibitors (TKI) in the treatment of lung cancer and *HER2* (tyrosine kinase ERBB2)-directed therapies in the treatment of *HER2* (human epidermal growth factor 2)-positive early-stage breast cancer as prime examples of success in the area of cancer pharmacogenomics [17]. A 2016 review of precision medicine approaches in oncology cites ALK (anaplastic lymphoma kinase) fusion oncogene and EGFR (epidermal growth factor receptor (EGFR)) mutations as the main molecular predictive biomarkers supporting NSCLC treatment [15]. Molecular testing for ALK fusion genes has proven valuable. Abbott Molecular already offers a multiplexed assay, the Vysis ALK Break Apart FISH Probe Kit, endorsed by the 2016 National Comprehensive Cancer Network (NCCN) NSCLC practice guidelines [15]. Though ALK fusion gene rearrangements are relatively rare (< 5% of NSCLC cases), clinical responses to targeted inhibitors (e.g., crizotinib) can be quite dramatic [5]. In favor of the precision medicine approach, excluding patients without these mutations can also minimize the exposure of patients to costly and potentially toxic therapies unlikely to benefit them.

EML4-ALK is the specific biomarker used in determining patient efficacy for the choice of a TKI agent such as crizotinib in the tertiary or after-the-cancer-has-arisen management of NSCLC [5]. A 2014 cost-effectiveness study on the use of *EML4-ALK* fusion oncogene testing in first-line crizotinib treatment for patients with advanced NSCLC reveals the complexity inherent in this precision medicine approach [18, 19]. The investigative team found that *EML4-ALK* testing to govern therapeutic decisions improved patient outcomes by an average of 0.011 quality-adjusted life-years (QALYs) while adding extra costs of $2,725 per patient, of which only $60 was attributable to the molecular assay itself. The overall interpretation of the cost-benefit calculus changes dramatically, however, when the cost of the companion drug (crizotinib) is considered. The incremental cost-effectiveness ratio is defined as the difference in cost between two alternative interventions, divided by the difference in their effect or impact. The incremental cost effectiveness ratio for administration of the drug itself was $250,632 per QALY gained. The investigators concluded that the regimen is “likely not considered cost-effective in the current setting” [19]. This assessment was unaltered when the

model was subjected to a sensitivity analysis of alternative costs for the molecular testing. States one reviewer, "Where companion diagnostic precision medicine is considered, these assays are by nature tightly coupled to the cost of the specific associated drug" [18].

Assays for EGFR inhibition may be used when other TKI inhibitors, such as gefitinib and osimertinib, are being considered for NSCLC therapy [15]. The U.S. Food and Drug Administration (FDA) has approved two multiplex assay kits, also NCCN endorsed, for this purpose – the *therascreen* EGFR RGQ PCR Kit (for use with gefitinib), and the cobas EGFR Mutation Test (for use with osimertinib). A cost-effectiveness analysis performed by an Australian team compared the use of combined multiplex testing and targeted therapy with NSCLC chemotherapy without testing, and thirdly with best supportive care without testing [20]. The combined strategy resulted in an additional 0.009 life-years (LYs) gained, compared to 1.458 LYs gained in the case of each of the other two strategies. The combined strategy resulted in an incremental cost-effectiveness ratio of $485,199 (Australian)/QALY comparing combined and best supportive care strategies, and $489,338 (Australian)/QALY comparing combined and chemotherapy only strategies. Decreasing test and test interpretation costs by half reduced the ratios, but they still remained greater than $200,000 (Australian)/QALY. The authors concluded that multiplex testing and targeted therapy is not cost-effective as a fourth-line treatment in metastatic lung cancer when first-line treatments such as chemotherapy without pharmacogenomics testing can be employed.

Other predictive biomarkers for NSCLC treatment are on the horizon. For example, *KRAS* mutations can suggest lack of therapeutic efficacy to EGFR targeted therapies. The FDA has cleared *KRAS* mutation detection assays for use in colorectal cancer, but such assays have not yet been approved for use in NSCLC [15].

The Precision Medicine Approach to Breast Cancer

Breast cancer is the most common cancer among American women. It is the second leading cause of cancer death in women, exceeded only by lung cancer [21]. About 85% of breast cancer cases occur in women with no family history of breast cancer. These cases are due to somatic cell mutations which occur as a result of aging, various exposures (such as pre- and postmenopausal hormone therapy), and other life events.

Precision medicine efforts for breast cancer due to somatic mutations fall into at least four categories, two of them – endocrine therapy and *HER2* therapy – being mainstay treatment categories. *HER2*-directed therapies, for which trastuzumab (Herceptin) is often used, are one of the two major pharmacogenomics successes in the cancer area cited by Ritchie [17]. Tamoxifen is a major drug of choice in the category of endocrine therapies, itself being a selective estrogen receptor modulator [15].

Herceptin has proven utility in reducing risk for cancer recurrence after surgery for early-stage *HER2*-positive (*HER2+*) breast cancer, and improving survival in late-stage (metastatic) *HER2+* breast cancer, but it also poses serious side-effects such as heart damage. Herceptin therapy can also cost a sizable amount, up to $50,000 per year [22]. Overexpression of the *HER2* gene (*HER2+* status) is associated with rapid tumor growth and negative diagnostic and prognostic indicators. A systematic review and meta-analysis performed in Canada compared seven different strategies employing immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) to determine *HER2* status, thus appropriateness of using Herceptin [22]. Each strategy utilized an IHC score (0, 1+, 2+, 3+) alone or coupled with FISH confirmation to form this inference. The incremental cost-effectiveness ratio was lowest when cases with an IHC score of 2+ or 3+ (as opposed to 0 or 1+) were confirmed by FISH, which yielded a ratio of $3,351 (Canadian)(minimum) to $12,230 (Canadian)(maximum) per accurately determined case. The cost-effectiveness analysis is favorable given that accurate assessment of *HER2* status is capable of reducing the cost of Herceptin therapy by $0.6 million per year, and saving $12 million per year in women who are *HER2-*, thus can be kept off Herceptin [22].

Estrogen-focused therapies have been a part of standard care for more than thirty years, and have displayed an evolution in policy analysts' thoughts about the gold standard for precision management [15]. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group was launched by the CDC Office of Public Health Genomics in 2004 to conduct systematic, evidence-based reviews of burgeoning genetic tests and other applications of genetic technologies in transition from research to clinical and public health practice. EGAPP has produced two systematic reviews of the use of gene expression profiling to improve therapeutic outcomes in women with breast cancer. EGAPP's 2009 review examined the validity and utility of three tests – Oncotype DX, MammaPrint, and the H:I (normalized gene expression) ratio [23]. These tests have been designed to go beyond the standard estrogen/progesterone receptor status indicator to predict tumor recurrence risk

for women on tamoxifen, for whom alternative therapies might be considered. The EGAPP Working Group found adequate evidence from the NSABP B-14 randomized controlled trial to support the association between Oncotype DX recurrence scores and 10-year distant metastases in estrogen receptor positive (ER+) patients, and adequate evidence to support the association between RS score and overall chemotherapy benefit, particularly for patients in the high risk category [23]. Recent publication of interim results for the TAILORx study has shown a further association between recurrence score and 5-year disease-free survival and distant recurrence in patients at low risk [24].

A follow-up systematic review by the EGAPP Working Group published in 2016 confirmed its previous findings but also noted the lack of direct evidence that the use of Oncotype DX improves clinical outcomes [25]. It also highlighted contradictory cost-effectiveness results in studies performed in the U.S. (for which $2,000 in cost savings per patient were due to a decrease in post-testing chemotherapy use) and the U.K. (for which an incremental cost-effectiveness ratio of 26,940 £/QALY gained were due to an increase in chemotherapy use) [25]. The U.K. National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee concluded that, under the assumption of equal chemotherapy benefit for all Oncotype DX risk categories, the test is not cost-effective at its current pricing level. In the first EGAPP review, data were adequate to support an association between the MammaPrint Index and 5- to 10-year metastasis rates, but the efficacy relative to classical clinical factors was unclear. More conclusive results await the completion of the MINDACT trial. For the H:I ratio test, populations studied were quite heterogeneous, and the test's commercial offering was based on a single study in women with primary, untreated breast cancer.

The Precision Medicine Approach to Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in both men and women in the U.S. [26]. It is the third leading cause of cancer deaths when men and women are considered separately, and the second leading cause in both sexes combined.

Considerable effort has been placed into targeted therapies and companion diagnostics for CRC. About 70-80% of patients present with resectable localized disease, treated by surgery and often followed by adjuvant therapy [27]. CRC patients with advanced disease may receive first-line chemotherapy, or chemotherapy and radiation before surgery is considered.

The EGAPP Working Group published in 2009 a systematic review of one first-line chemotherapeutic agent, irinotecan, which may be accompanied by *UGT1A1* genotyping to check for ability to adequately clear the drug [27]. Such genotyping aids decisions to either increase drug dose for more aggressive therapy, or switch to common alternate drugs, bevacizumab or cetuximab, for instance, in individuals with reduced clearance at risk for adverse events. EGAPP had two major findings: (1) unless patients receive a certain threshold dose of irinotecan, the increase in risk for toxicity is not significant, thus testing may not be warranted; and (2) reducing the dose of irinotecan (personalized dosing) to avoid adverse events may lead to more cases of unresponsive tumors than instances of adverse events avoided. It is inconclusive that benefits outweigh harms in the application of a precision approach here.

The alternate drugs mentioned above are positioned among the three main classes of targeted therapies approved for metastatic CRC: (1) multikinase inhibitors; (2) angiogenic inhibitors; and (3) anti-EGFR antibodies [15]. Up to 50% of CRC patients respond to anti-EGFR therapy, which includes cetuximab [28]. *KRAS* wild-type status is considered an important factor in achieving a clinical response from this category of therapy [29]. However, 40-60% of patients with wild-type status do not respond to such therapy. Data suggest that *BRAF* gene status also plays a role in anti-EGFR response, and that the *BRAF* V600E mutation, present in 5-10% of CRC tumors, can lead to a positive response. To date the FDA has cleared two genetic testing kits, the *therascreen* KRAS kit from Qiagen, and the cobas KRAS Mutation Test from Roche [15]. The American Society for Clinical Oncology (ASCO) and three other professional organizations released new consensus guidelines in 2015 strongly recommending *KRAS* mutational testing for patients being considered for anti-EGFR therapy, and that *BRAF* V600 testing also be considered.

The EGAPP Working Group conducted a systematic review of companion diagnostic use of *KRAS* and *BRAF* mutation testing in anti-EGFR therapy in 2013 [30]. The systematic review looked at multiple pooled assessments, each consisting of up to seven studies, which together indicated statistically significant increased response rates to cetuximab and other anti-EGFR drugs, reduced risk of disease progression, and enhanced overall survival with *KRAS* wild-type status. EGAPP cited a cost-effectiveness study of *KRAS* testing in metastatic CRC patients in the U.S. and Germany [30, 31]. For the U.S. patients, use of *KRAS* testing to select patients for EGFR inhibitor therapy saved $7,500 to $12,400 per case. A second cited study from Japan displayed an incremental cost-effectiveness ratio for cetuximab with *KRAS* testing to be

$180,000 per QALY gained compared to therapy without testing [32]. Due to this cost, the investigators concluded that the protocol was not cost-effective, even when treatment was limited to patients with wild-type *KRAS*. Two of three studies looking at *BRAF* testing found associations similar to the *KRAS* studies in terms of progression-free and overall survival, but these findings, however, were not contingent on whether or not cetuximab was included in the combination therapy. Thus, while the review supported recommendations for a precision approach using *KRAS* mutation testing, it found insufficient evidence to link *BRAF* V600E mutation testing with treatment response independent of prognostic association.

Table 1 summarizes the cost-effectiveness and descriptive findings for the pharmacogenomics or companion diagnostic precision medicine approach to the three cancers.

Table 1. Pharmacogenomic/Companion diagnostic approach – 3 cancers

Condition	Therapy	Biomarkers	Cost-Effectiveness	References
Non-small cell lung cancer (NSCLC)	Tyrosine kinase inhibitors	*EML4-ALK*	$255,970/QALY gained	Djalalov et al. [19]
		EGFR	$489,338 (Austr.)/QALY gained	Doble et al. [20]
HER2+ Breast cancer	Herceptin	IHC, FISH	$3,351 – 12,230 (Can.) saved per case	Dendukuri et al. [22]
ER+ Breast cancer	Endocrine	21-gene assay	26,940 £ (Brit.) cost/QALY gained	EGAPP [25]; Ward et al. [33]
Metastatic colorectal cancer	Topoisomerase 1 inhibitor (TOP1) – irinotecan	*UGT1A1* genotyping	ambivalent results – reducing toxicity vs. reducing tumor burden	EGAPP [27]
	Anti-EGFR	*KRAS*	$7,500 – 12,400 saved per case	EGAPP [30]; Vijayaraghavan et al. [31]
			$180,000/QALY gained	EGAPP [30]; Shiroiwa et al. [32]

TAKING PRECISION MEDICINE BEYOND THE PERSONALIZED LEVEL

One argument against the informativeness of the above studies is that they represent a personalized medicine approach, but not a precision medicine approach in its full capacity [3]. The electronic storage of information, which can be multifactorial, including relevant lifestyle, would seem to be crucial to maximizing benefits and minimizing cost. The investigative team looking at the infrastructure characteristics of the Lee Moffit Cancer Center "Total Cancer Care" program also examined six other major healthcare programs engaged in cancer care comparative effectiveness research in genomic and precision medicine [10]. Four of the researched programs – at Duke University, Kaiser Permanente, University of Pennsylvania, and the Fred Hutchinson Cancer Center – had established a complex infrastructure (with data and biospecimen registries and multidisciplinary research teams), were engaged in "knowledge generation" (via randomized controlled trials and observational studies), and had reached the stage of "knowledge synthesis" (horizon scanning, evidence synthesis, and decision modeling). These programs display a depth of information and range of multidisciplinary expertise that is reflective of the type of knowledge synthesis of which the PMI's million person cohort will be capable.

The Duke University and Kaiser Permanente teams noted a number of strategic challenges to the amassing of cancer study data – limited data quality, large variation in genomic methodology used, and poor demonstration of clinical utility for the genomic tests supplying the data [10]. These observations point out challenges that could foreseeably face PMI investigators attempting to collate information from the expansive precision medicine cohort. The Kaiser Permanente group was able to show that in screening for Lynch syndrome, a hereditary form of CRC, microsatellite instability testing (MSI) was preferable compared to immunohistochemical staining (IHC). In the treatment phase, the investigators found that screening for *KRAS* and *BRAF* mutations improved the cost-effectiveness of anti-EGFR therapy, but that the cost of the therapy surpassed generally accepted cost-effectiveness thresholds of $100,000/quality-adjusted life-year. These findings allude to the capability of the PMI to develop new data on useful oncogenomic screening, mutational testing, and therapeutic procedures, and to the correspondingly likely possibility that many of the discoveries, while being

individually beneficial, could elude effectiveness for the clinical population as a whole.

The PMI will no doubt be carried in new directions that have not yet been quantified, however. NCI is engaged a new type of clinical trial called "NCI-MATCH" [34]. In this innovative program, adult cancer patients are assigned to targeted treatments based on the genetic abnormalities in their tumors, regardless of the type of cancer they have. This concept represents the therapeutic end of what has been happening with diagnostics. *KRAS* and EGFR mutation testing is now occurring for multiple cancer types. Why should cancer therapies be restricted to just one cancer type? New management models may also evolve. The data infrastructure supporting precision medicine can and is being used to develop procedural algorithms that combine genetic testing with genetically targeted therapies. These algorithms, if tailored to the lay person, can then be used by both medical providers and patients in collaboration, improving the effectiveness of the prescribed regimen. Shen and Hwang use *CYP2C9* (they cite *CYP450*) testing for warfarin dose performed at home first by nurses then by patients as an example [6]. This linkage of "big" or "rich" data and the development of new, useful algorithms is cited by multiple authors [2, 5, 35]. The issue is whether providers of various types, and consumers, can understand the test results and appreciate the connection to one-size-does-not-fit-all therapeutic management [36].

Authors discussing the translation of big data into usable guidelines and algorithms are not just limiting the payoff to individualized treatment, however. Jameson and Longo, for instance, speak of not just a pharmacogenomic future, but one in which "guideline-based screening", e.g., colonoscopy, can be targeted on the basis of age and family history [5]. Family health history is one of several tools, including individualized genetic testing and family cascade testing, fueling the public health drive towards precision interventions [37, 38].

The public health approach to precision medicine, or "precision public health", is highly evidence-based. Precision public health is exemplified in the Centers for Disease Control and Prevention's emphasis on the implementation of Tier 1 genetic tests that have passed systematic review for analytic and clinical validity and utility – family history-based hereditary breast and ovarian cancer (HBOC) genetic testing (*BRCA1/2* mutations in relatives), and hereditary nonpolyposis colorectal cancer genetic testing (Lynch syndrome *MLH1, MSH2, MSH6, PMS2, EPCAM* mutations) [39]. Indeed, genetic counseling and testing for HBOC are already incorporated into healthcare

reform as services not requiring co-pay for individuals deemed at risk by their providers [40]. The PMI promises much more, however, and part of the vision of public health is that precision techniques can be used to direct genetic preventive strategies to those subsets of the population that will derive maximal benefit [41].

PUBLIC HEALTH INTERVENTIONS AND COST-EFFECTIVENESS

The Precision Public Health Approach to Lung Cancer

It has been remarked that "although personalized treatments can help save the lives of sick people, prevention applies to all" [3]. This comment applies especially to lung cancer, which can be tackled as we have seen individually and after it has manifested, or by using a preventive, population-based approach. Initial genome-wide association studies (GWAS) published by several investigative teams in 2008 were suggestive of lung cancer susceptibility genes being situated on the long arm of chromosome 15 [42]. The studies were all large (3,500 to 14,000 participants) and replicated, yielding strong evidence for an association between SNP variations at 15q24/15q25.1 and lung cancer. Thorgeirsson et al. found a highly significant association ($P = 1.5 \times 10^{-8}$) between a common variant in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 and smoking frequency, with an odds ratio of 1.31 (1.19 – 1.44, 95% C.I.) between nicotine dependent cases and low quantity smokers plus population controls [43]. Studies by Hung et al. [44] and Amos et al. [45] found odds ratios between 1.21 and 1.77 for associations between the nicotinic acetylcholine receptor regions 15q25 and 15q25.1 and lung cancer in ever smokers, the former accounting for 14% (attributable risk) of the lung cancer cases in the first study. The second study examined 2,724 NSCLC cases, the same type of cancer being treated in later stages by pharmacogenomics regimens.

More recent GWAS in never-smoking Asian females have pointed out genetic associations independent of smoking status. Case-control studies of never-smoking Asian females funded through the National Institutes of Health [46] and the Mayo Foundation [47] have identified genetic variants in the 3q28 and 13q31.3 regions associated with risk for lung cancer (N = 754 to 7,254 participants). These associations show both statistical significance ($P = 10^{-6}$ to

10^{-8}) in terms of odds ratios and allelic risk, and biological plausibility (association with the regulation of cell proliferation and division). These two lines of discovery – lung cancer in connection with nicotine dependence and independent of it – could beneficially lead to both personalized smoking-cessation interventions, and to increased screening of people at risk for lung cancer [41]. The difficulty is that the association studies are at the primary research (T1) stage and do not yet imply clinical validity.

Precision medicine in public health terms involves targeting groups at risk. Various professional societies have developed guidelines for lung cancer screening, generally beginning at age 55 [48]. The NCCN lung cancer screening guidelines recommend screening individuals age 50-55 years, those who have between 20 and 30 pack-years of exposure, and who exhibit one additional risk factor, such as family history. The relative risk of developing lung cancer is 1.8 if the individual has at least one first-degree relative with lung cancer, and 3.0 given two first-degree relatives with the condition [49]. The positive and negative predictive values for lung cancer appearing in a proband's first-degree relatives are 89.9% and 99.1%, respectively [50]. In the Utah Family High Risk Program, the cost of taking a family health history varied between $10 and $25 depending upon receipt of follow-up educational interventions [51]. These figures indicate cost-effectiveness for the use of family history in risk assessment for lung cancer.

Public health programs are especially concerned with the rights and welfare of underserved groups, an aim that is built into public health codes of ethics [52]. Surprisingly, of the 58,160 lung disease studies published between 1993 and 2013, less than 5% reported the inclusion of minority participants [53]. NIH is presently consulting researchers adept at recruiting under-represented groups into studies as part of PMI Research Cohort formation. An admixture study of 1812 African Americans performed by the Karmanos Cancer Institute in Detroit, MI demonstrates what can come out of the use of the PMI Cohort. Excess African ancestry was observed on chromosome 3q among ever smokers with NSCLC, a chromosomal region identified by previous studies with mostly persons of European ancestry [54].

The Precision Public Health Approach to Breast Cancer

About 10 to 15% of women diagnosed with breast cancer have germline mutations in the *BRCA1* or *2* genes. Between 10 and 30% of women under age 60 diagnosed with triple-negative breast cancer (cancer which does not have

receptors for estrogen, progesterone, or *HER2/neu*) display a *BRCA1/2* mutation [55]. Ashkenazi Jewish ancestry confers an increased risk, though such mutations are by no means relegated to just one group. Like lung cancer, the public health approach to hereditary breast and ovarian cancer (HBOC) focuses on primary prevention before disease has appeared. Primary prevention can be conducted through a variety of means, several of which fit under a public health precision model. A study out of the Cleveland Clinic Genomic Medicine Institute compared two methods for cancer risk assessment – "family history-based risk assessment" and "DTC [Direct-to-Consumer] personal genomic screening," the latter using a variety of risk alleles [56]. Of 22 high risk females appearing in clinic, family history classified eight individuals as being at risk for breast cancer, but only one of the eight was classified as high-risk through personal genomic screening method.

Family history is a quick way of identifying risk, and has value in this instance as it does with lung cancer. Valdez et al. note that the relative risk of developing breast cancer is 1.8 and ovarian cancer 2.9 if the individual has at least one first-degree relative with these conditions [49]. It is 3.0 and 14.7 given two affected first-degree relatives. The positive and negative predictive values for these cancers appearing in a proband's first-degree relatives are 89.1% and 98.9% for breast cancer, and 76.1% and 99.3% for ovarian cancer [50]. The U.S. Preventive Services Task Force (USPSTF) has conducted evidence reviews of genetic testing for the key mutations involved in HBOC, *BRCA1* and *2*. It recommends:

> Primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. [57]

The CDC-OPHG classifies the use of family history of known breast/ovarian cancer with deleterious *BRCA* mutations as Tier 1 [39]. CDC defines Tier 1 genetic interventions as those supported by clinical practice guidelines based on thorough systematic review. These modalities are ready for implementation not just on the individual but on the level of the at-risk population as well [38].

Family history, however, is part of a train of diagnostic interventions, including genetic counseling and genetic testing. The latter can lead to annual screening via MRI or to surgery. A 2012 cost-effectiveness analysis of *BRCA1/2* testing of women >= 35 years at elevated risk of carrying a mutation, considering the eventual use of these MRI and surgery, determined genetic testing to be cost-effective if testing cost were <= $8,948 [58]. Currently targeted *BRCA1/2* mutation testing ranges from $4,500 to $650 [58, 59].

Economies of scale operate when identifying persons at risk for cancer. Identifying single individuals can be expected to be less efficient than pinpointing families at risk, just as using information reflecting population risk data can be expected to be more efficient than utilizing separate family histories. Cascade screening is the testing of successive test positive family members starting with a positive index case. Two studies delineate that the success of *BRCA1/2* cascade screening in affected families, as measured by actual uptake of genetic testing, is a function of ability of family members to communicate with one another, and to attend a clinical session [60, 61]. Uptake rates of 54% (Utah study) and 73% (Manchester portion of U.K. study) were achieved when these conditions were satisfied. The London portion of the U.K. study, which covered a more dispersed population, achieved 62% for those clinically seen. George et al. indicate that the cost of *BRCA* testing in 30 at-risk relatives can be brought down from a minimum of $66,000 to $12,000 once the responsible mutation has been identified in a family member [62].

On a population level, it is possible to gather information on early-stage breast and ovarian cancer, and to report aggregate information back to participating institutions. A breast cancer incidence study utilizing the Connecticut Tumor Registry found that the ability to detect cases depends on the relative population size of the groups being assessed (here white versus nonwhite) [63]. Population-based risk assessment has the advantage of detecting *BRCA1/2* carriers with a negative family history. Clinical validity goes up with the prevalence of a disorder in a given population. Rubinstein et al. performed a decision analysis of *BRCA1/2* testing in American Ashkenazi Jewish women aged 35-55 years [64]. At a cost of $460 for founder mutation testing, the investigators concluded that such a program is cost-effective, amounting to $8,300/QALY gained.

The PMI, like state cancer registries, is especially geared towards targeting at-risk individuals and populations. The CDC notes that state health departments have engaged in bidirectional reporting, i.e., identification of cases from the state tumor registry, and reporting back of information to participating facilities. The Michigan Department of Health and Human

Services and Connecticut Department of Health have both identified thousands of cases of breast and ovarian cancer suggesting risk for HBOC, and returned back facility-specific data [65]. In the case of Connecticut, facility-specific reports on numbers of breast and ovarian cancers, compiled from 3,792 cases in the state cancer registry, were reported back to providers to alert them that patients might be at an increased risk for HBOC. Staff at 70% of the 32 involved hospitals also requested and received an HBOC training session.

In the age of electronic health records (EHRs), systems can be designed to provide physicians with decision support tools that alert them to the need for genetic testing, and assist with interpretation of results and potential impact on patients and their families [11]. It is also possible with EHR systems to flag patients who are members of high-risk families to make them aware of their risk status and available options [66, 67].

The Precision Public Health Approach to Colorectal Cancer

The hereditary form of CRC that has received the most public health and medical attention is hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome (LS), which produces only a small number of polyps or none at all. LS is the most common heritable cause of CRC, representing 1 in 35 cases [66]. Whereas the lifetime risk for developing CRC is 2 to 5% in the general population, it is 80% in those with LS.

Family history as an instrument for performing cancer risk assessment in first- and second-degree relatives is even more accurate for CRC than for the other two families of cancers. Valdez et al. report that the relative risk for CRC is 2.2 given a first-degree relative with the condition, and 4.0 given at least two first-degree relatives with CRC [49]. Lynch syndrome is notoriously underdiagnosed, however. The vast majority of families with a history of CRC do not know they may have LS, or even that a genetic test is available [66]. Nevertheless, the EGAPP Working Group, using a chain of evidence methodology comparing four preliminary testing (MSI, IHC, and *BRAF*) and mismatch repair (MMR) gene strategies leading to medical and surgical management, found that adequate evidence exists that an appropriate testing strategy can improve clinical outcomes for patients and their families [68].

A precision public health approach to Lynch syndrome entails spotting cases before the management is made more complex by disease advancement,

coupled with identifying at-risk relatives free of disease. A 2014 consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer looked at initial approaches for index case identification. Use of clinical criteria (e.g., the Revised Bethesda Guidelines) and a CRC risk assessment tool using family history – "selective approaches" used to identify a range of patients – both showed adequate sensitivity in identifying individuals with germline mutations, but up to 28% of LS patients can be missed with a liberal interpretation of the revised guidelines [69]. A more "universal approach" assessing LS risk based on IHC testing of all incoming cases of CRC was found to have greater sensitivity than selective strategies including the use of the Bethesda guidelines. Such an approach is still shy of being considered population-wide risk assessment in that testing begins with confirmed colorectal cancer cases. Multiple studies have shown that: (1) the systematic application of testing among patients with newly diagnosed CRC could provide substantial clinical benefits at acceptable costs; and (2) adopting a "universal" approach towards CRC genetic testing is cost-effective [69]. Palomaki et al., for example, found that a strategy employing IHC and *BRAF* preliminary testing followed by MMR mutation testing in *BRAF* negative cases would cost an average of $18,863 per LS case detected [70].

Having identified an index case, the public health approach is then to move on to relatives to identify those at risk for LS, and those who are not. The EGAPP Working Group cites seven studies showing how uptake of colonoscopy by relatives with LS ranged from 53 to 100% [68]. Sharaf et al., in a sub-analysis of four select articles from a broader LS studies review, concluded that 52% or less of the first-degree relatives received LS genetic testing [71]. This number was critiqued by Jasperson, who noted that the Sharaf analysis excluded a large study containing 466 family members composed almost exclusively of first-degree relatives at high-risk of developing LS [72]. The latter study found 75% of the members to have been tested for LS mutations.

The cost of cascade testing is also a consideration. The per mutation cost of MMR gene testing for LS can decrease from $1,000 to $350 once a specific familial mutation has been identified in the proband [59]. The consequence is that the cost per LS index case can decrease from $18,863 to $13,000 [68]. In the most comprehensive cost-effectiveness assessment of universal and "near-universal" genetic screening to date, covering seven LS studies that also looked at medical/surgical follow-up and testing of relatives, Grosse found that all except one reported incremental cost-effectiveness ratios less than the

threshold $100,000 per life-year or quality-adjusted life-year gained [73]. As with HBOC, collection and reporting of LS data has occurred at the state level. Michigan identified 10,000 CRC cases from its cancer registry, and returned facility-specific data and educational materials to 145 reporting institutions [74]. Connecticut reported back information on 3,517 CRC cases in its cancer registry to targeted practitioners at acute care hospitals. These bidirectional reporting efforts show that health-related information may be stored *en masse* for both practical and research purposes (as in the PMI Cohort), and can be reissued for clinical and public health purposes.

Table 2. Public health precision approach – 3 cancers

Condition	Genetic test	Cost-effectiveness	References
Familial lung cancer	Family history (FH)	*FP rate: 1.9 (female) – 6.1 (male) FN rate: 29.1 (female) – 37.5 (male) **PPV: 81.0 (68.6 – 90.1)*** NPV: 97.1 (96.0 – 98.0)	Ziogas and Anton-Culver [50]
		Cost $10 – 25/FH taken	Johnson et al. [51]
	GWAS – remains investigational		
Hereditary breast and ovarian cancer (HBOC)	*BRCA1/2*	Cost-effectiveness threshold $8,948 (current testing $650 – 4,500)	Goodman [58]
		$8,300/QALY gained (U.S. Ashkenazi population)	Rubinstein et al. [64]
Hereditary nonpolyposis colorectal cancer (Lynch syndrome – LS)	Multi-gene testing (*MLH1, MSH2, MSH6, PMS2, EPCAM*)	$18,863 cost/index case $13,000 cost/relative	EGAPP [68]; Palomaki et al. [70]
		$29,600 – 63,900/ QALY gained ("universal" testing)	Grosse [73]

* False positive (FP) and false negative (FN) rates.
** Positive predictive value (PPV) and negative predictive value (NPV).
*** 95% Confidence interval.

The Colorado Department of Public Health and Environment also targeted educational outreach relating to hereditary CRC to 430 medical providers and 200 at-risk cases [74]. A survey was conducted which showed that 98% of provider and patient respondents thought that the information was clear and useful, many patients having indicated they engaged in further dialogue with their physician, a genetic counselor, or a family member. About 1/3 of the patient respondents communicated that they planned to have a risk assessment as a result of receiving the materials. The Colorado educational efforts were conducted by mail. An extensive, 33-study article review by Naylor et al. found that further patient education involving phone or in-person contact combined with patient navigation of resources can lead to improvements on the order of 15% in colorectal screening rates in minority populations [75].

Table 2 outlines the array of precision public health efforts, which involves targeting of screening, genetic testing, and education for the three cancer conditions.

CONCLUSION: CONTINUITY AND EMERGENCE IN PRECISION HEALTH APPROACHES

A major point brought out by the two tables is that pharmacogenomic regimens cost considerably more than primary prevention approaches to cancer management. From the articles reviewed herein, the former often exceed cost-effectiveness thresholds, though this conclusion need not necessarily be true for the regimens that are being offered. The cancer drug being prescribed is typically the main contributor to the cost, as opposed to the companion diagnostic, which can actually bring the price down. One can then view this conclusion in three ways: (1) optimistically, economies of scale or institutional policy changes might ultimately bring the cost of the pharmacogenomic regimen down; (2) the value of a person's life is to be held paramount, thus the costs incurred, from a private perspective, are worth it; or (3) the value of the primary prevention approach, due to its cost-effectiveness, is to be emphasized.

The medical and public health approaches are not to be viewed as mutually exclusive. Their territories are more like the circles of a Venn diagram which intersect with plenty of shared space in the middle. Both the CDC and its EGAPP program have devoted considerable attention to

companion diagnostics and the attempt to prove that they have overall utility, including cost-effectiveness. Public health has an evaluative role that dips into hospital-based interventions. The national view is more one of mergence [3]. The fact that *BRCA1/2* genetic testing takes off where chemotherapeutic approaches to breast cancer leave off, in terms of the host cancer's hormone receptor status, indicates that the domains of the primary/secondary and tertiary prevention camps are complementary. It would be idealistic to assume that predictive genetic testing plus monitoring could eliminate all tumors before they spread. Both ends of the prevention continuum are needed, and the more targeted they are, the better. It is also important to recognize that the medical and public health approaches both defy stereotyping. The use of *KRAS* testing in anti-EGFR therapy of metastatic colorectal cancer can be cost-saving. The value of a public health approach genetic to lung cancer is limited by the current state of GWAS findings and the heavy influence of gene-environment interactions in the genesis of lung cancer. Indeed, some would argue that federal and state policy approaches towards smoking and lung cancer should take center stage.

Policymakers have a role in deciding allocation of healthcare dollars. In providing arguments for and against utility in this paper, we are not advocating a withdrawal of dollars from either medical or public health oncogenomic approaches. The case has been made for a more detailed consideration of the proportion of dollars that go towards prevention, however. The paper has not dealt just with chemotherapy, or just with Tier 1 genetic testing, however – emphasis has been placed on a precision approach for both. In public health, this nuance translates into tailoring the intervention towards communities at-risk or in-need. It will be more cost-effective thereby, and will achieve the ethical standard of addressing the health of all by attending to those most in need.

A final point should be made about the medical and public health precision approaches that are emerging. The medical approach is showing healthy signs of growth. The PMI Research Cohort will grant it the ability to host more clinical trials with suitable cohorts of participants, and to speed up the process of conducting clinical trials. As NCI plans, some of these trials will cross typological borders and target treatments based on somatic abnormalities in the tumors regardless of cancer type [34]. Public health research will also benefit from the PMI Cohort, especially in instances where major germline mutations have not turned up and GWAS are actively identifying lower risk alleles having a cumulative effect. Given the thought being given to participating groups, the discovery of new risk alleles will most

certainly benefit diverse communities. The promise of tapping into lifestyle and environmental factors as data on the cohort participants builds will strengthen prevention approaches even further. The word "precision" also applies to the educational component of health programs. Educational efforts can become more tailored to the needs of at-risk groups as the data accumulates. Precision public health does not end with the target molecule, but with the whole person and the community to which he or she belongs.

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