Abstract

Personalized Medicine evolved from the genomics era and allows disease prediction based on genetic mutation, and development of individualized health care, both preventive and responsive, as a consequence of a patient's own genetic features. Personalized medicine for cancer is similarly proactive and individualized, based on genetic information and used to manage cancer risk and disease for solid and lymphoproliferative cancers, those with a hereditary basis and those arising spontaneously. In the developing world, cancers now kill more people than infectious disease and while many resource-limited countries still lack basic facilities to care for cancer patients, middle-income countries, such as Panama, are beginning to make simple applications of personalized medicine for cancer diagnosis and treatment. These applications focus on cancers which affect the greatest number of people and those for which proven tests and therapies already exist. Three such cancers are lung, breast and colorectal cancers, which have similarities in the biochemical dysfunctions at their foundations. A limited and affordable portfolio of genetic tests could be established by developing world diagnostic laboratories to aid oncologists in risk assessment, diagnosis, prognosis and pharmaceutical choice in the personalized management of cancer. The establishment and clinical use of these tests in developing world nations will require innovative models of financing and strengthening of human resources and technical and legislative infrastructure.

Keywords: Panama, Individualized Medicine, Genetic Testing, Medical Oncology, Developing World

Introduction

Personalized Medicine is an advance in patient care arising from genomics. At its foundation is our capacity to read and analyze an individual's genome, allowing identification of changes in the genetic code that correlate with a phenotype of increased disease risk. While practicing medicine has always been "personal" in nature, with a physician responding to the specific medical needs of a specific patient in a specific way which is standard for the disease condition presented, personalized medicine is distinguished from traditional care in two ways. Firstly, it precisely predicts disease occurrence based on changes in the genetic code that correlate with a phenotype of increased disease risk. While personalized medicine for cancer in the developing world
the Human Genome Project in 2000. For the first time, scientists and physicians could read the entire human genetic code and begin to correlate genotype with phenotype, for disease conditions and other traits. Since 2000, when one genome was sequenced for approximately 3 billion USD (1), decreasing sequencing costs have led to the very real prospect of sequencing a human genome for less than 1000 USD (2, 3). A handful of high profile artists, scientists and religious figures have already had their own genomes sequenced to publicize various health issues and initiate discussion on genomic technology and its ethical implications (4). Some genomicists predict we will have the capacity to sequence every human genome at birth within the next 10 years.

Until the time that genome sequencing for disease prediction is routine in patient management, however, personalized medicine must take a broader definition. The first major textbook on genomics and personalized medicine suggests it is characterized by “the use of predictive tools to develop a new model of health care based on health planning that is proactive and preventive”, compared to traditional medicine, which is “reactive, episodic and geared towards acute crisis intervention once disease is already manifest and largely irreversible” (5). The National Cancer Institute recognizes personalized medicine as “a form of medicine that uses information about a person’s genes, proteins and environment to prevent, diagnose and treat disease” (6) and the Jackson Laboratory notes that personalized medicine “shifts the emphasis in medicine from reaction to prevention; predicts susceptibility to disease, improves disease detection and preempts disease progression; customizes disease-prevention strategies; prescribes more effective drugs and avoids prescribing drugs with predictable side effects; reduces the time, cost, and failure rate of pharmaceutical clinical trials, and eliminates trial-and-error inefficiencies that inflate health care costs and undermine patient care” (7).

**Personalized medicine for cancer:** Personalized medicine for cancer is similarly based on the foundations of prediction and prevention. By using information on personal genetics and environment, management of cancer risk and disease can be proactive and individualized. Cancers with underlying hereditary or infectious cause and those arising sporadically will all benefit from applying personalized medicine in the form of genetic and genomic testing, followed by clinical surveillance or therapy specifically appropriate to the individual’s genetic information. Standard community-based screening and diagnostic programs, such as those for bowel, cervical, breast and prostate cancer, can now be complemented by such gene-based tests, which are available for pre-symptomatic risk assessment of cancer, as well as diagnosis, prognosis and treatment optimization for a number of solid and lymphoproliferative malignancies (7).

**Cancer in the developing world:** Of the 12.6 million new cases of cancer and 7.5 million cancer deaths, every year, world-wide (8), 56% of cases and 64% of deaths occur in low- and middle-income countries (9). Not only is the burden of cancer mortality and morbidity higher in developing countries (Table 1), but individual cancer risk, currently higher in the developed world, is also increasing in the developing world (10).

In low- and middle-income countries, increased risk of cancer and cancer death arises from exposure to carcinogens including alcohol, cigarette and fire smoke, and oncogenic infectious agents, thought to cause 20% of cancer in these nations (11); the presence of specific racial groups with higher cancer susceptibility due to genetic background (discussed below); increasing longevity from improved nutrition, infectious disease control, maternal-child health programs, and economic growth and political stability; and perhaps most significantly, decreased and delayed diagnosis and treatment options (12).
In at least thirty low- and middle-income countries, cancer diagnosis and treatment are retarded due to the absence of basic resources, such as tools to analyze Pap smears, radiation therapy machines and trained technicians and oncologists (12). In these countries, a primary goal in caring for cancer patients has been to establish essential physical and human infrastructure, a task being supported by the IAEA’s Programme of Action for Cancer Therapy (13). A second goal is ensuring that basic programs for cancer prevention are established and promoted: vaccination campaigns against Hepatitis B and Human Papillomavirus; public education campaigns against smoking and excessive alcohol consumption; control of malaria, co-implicated with Epstein-Barr virus as the underlying cause of African Burkitt’s lymphoma (14); and screening programs for cervical and breast cancer, as well as for *Helicobacter pylori* and liver fluke, significant contributors in some regions to gastric and liver cancer, respectively (14). In these nations, furthermore, while cancer causes more deaths than malaria, tuberculosis and HIV/AIDS combined, health care priorities may justifiably be focused elsewhere than cancer for some years to come (15).

In middle-income countries, however, where basic laboratory, clinical and public health infrastructure and cancer-care services already exist, there is clearer justification for investing in personalized medicine for cancer. One such country is Panama, a country of approximately 3 million people in Central America whose rates of cancer death and incidence and the likelihood of survival from cancer still more closely resemble the developing world than the developed world (Table 1). The application of personalized medicine for cancer in Panama will be our case study in this paper.

**Priorities for personalized medicine for cancer in the developing world**: Personalized medicine for cancer in resource-poor countries needs to be considered relative to other health and cancer goals and applied on three criteria. The first concerns the impact of the cancer on society, focusing personalized medical efforts on cancers with the highest incidence of morbidity and mortality, those predominantly affecting young people and cancers for which survival rates are lower in the developing world than in the developed world. The second prioritizes cancers for which genetic testing has been proven reliable and effective, which is based on high-penetrance genes, and whose application in the developing world can be justified on the basis of improving patient survival and quality of life for the greatest number of people, with small initial investments in technical infrastructure to establish their use. The third prioritizes cancers for which therapy will be reliably and affordably available in the long-term.

Considering the first criterion, it is relatively simple to prioritize cancers which demand attention based on statistics of incidence and death. In the developing world, cancers with the highest incidence of death overall, and for men specifically, are lung/bronchial, liver, stomach, esophagus and colorectal cancers, with breast and cervical cancers also being important causes of cancer death for developing world women (Table 2). In the middle-income country of our case study, Panama, other adult cancers of significance for their rates of incidence or mortality are prostate cancer, leukemia, Non-Hodgkin lymphoma and brain and nervous system cancers. In children of less than 14 years, significant causes of cancer in low- and middle-income countries are leukemia, Non-Hodgkin lymphoma, brain and nervous system cancers, kidney cancer and Hodgkin lymphoma (16). The likelihood of surviving cancer in the developing world is decreased for Hodgkin and non-Hodgkin lymphoma; multiple myeloma; thyroid, prostate and testicular cancer, or if you are less than 14 years of age (Table 3). Survival rates for other, high incidence cancers of the developing world, such as lung and liver, are similar to rates for the developed world, for reasons explained below (Table 3). The second criterion which prioritizes genetic tests and personalized therapeutics...
Table 1. Cumulative burden (%) of cancer deaths and incidence, and likelihood of survival by age group compared for less and more developed countries. Raw data taken from IARC (16) and comparisons were performed using the GLOBOCAN Online Analysis - Age-Specific Tables tools, using Population as Less Developed, More Developed or Panama; Sex as Both Sexes; Data Type as Incidence or Mortality; and Statistic as Numbers. ‘Deaths’ and ‘Incidence’ expressed as the cumulative percentage of deaths (or incidences) occurring due to cancer in defined age groups. ‘Crude likelihood of survival’ calculated as [1-total number of deaths/total number of incidences]. Relative likelihood of survival calculated as [Crude likelihood of survival for Less developed countries or Panama/Crude likelihood of survival for More developed countries].

<table>
<thead>
<tr>
<th>Age</th>
<th>Deaths Less developed (%)</th>
<th>Deaths More developed (%)</th>
<th>Deaths Panama (%)</th>
<th>Incidence Less developed (%)</th>
<th>Incidence More developed (%)</th>
<th>Incidence Panama (%)</th>
<th>Crude likelihood of survival Less developed</th>
<th>Crude likelihood of survival More developed</th>
<th>Crude likelihood of survival Panama</th>
<th>Relative likelihood of survival Less developed</th>
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<th>Relative likelihood of survival Panama</th>
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<td>83.3</td>
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<td>100.0</td>
<td>0.05</td>
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<td>0.38</td>
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Table 2. Leading causes of cancer cases and deaths compared between less developed and more developed countries. Data summarized from IARC (16).

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<tr>
<th>Cancer type</th>
<th>Less developed country deaths</th>
<th>Less developed country cases</th>
<th>More developed country deaths</th>
<th>More developed country cases</th>
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<tr>
<td></td>
<td>Overall</td>
<td>Men</td>
<td>Women</td>
<td>Overall</td>
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<tr>
<td>All sites but skin</td>
<td>4,810,100</td>
<td>2,697,500</td>
<td>2,112,600</td>
<td>7,107,600</td>
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<td>Lung &amp; bronchus</td>
<td>778,000</td>
<td>539,000</td>
<td>239,000</td>
<td>884,500</td>
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<tr>
<td>Liver</td>
<td>580,600</td>
<td>402,900</td>
<td>177,700</td>
<td>626,700</td>
</tr>
<tr>
<td>Stomach</td>
<td>556,400</td>
<td>353,500</td>
<td>202,900</td>
<td>713,900</td>
</tr>
<tr>
<td>Esophagus</td>
<td>338,900</td>
<td>223,000</td>
<td>115,900</td>
<td>400,500</td>
</tr>
<tr>
<td>Colon &amp; rectum in</td>
<td>288,500</td>
<td>154,400</td>
<td>134,100</td>
<td>506,400</td>
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<tr>
<td>Breast</td>
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<td>0</td>
<td>268,900</td>
<td>691,300</td>
</tr>
<tr>
<td>Cervix uteri</td>
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<td>242,000</td>
<td>453,300</td>
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<tr>
<td>Leukemia</td>
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<td>95,100</td>
<td>75,100</td>
<td>209,900</td>
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<td>Prostate</td>
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<td>121,900</td>
<td>0</td>
<td>255,000</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>120,100</td>
<td>71,600</td>
<td>48,500</td>
<td>175,200</td>
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<td>Brain, nervous system</td>
<td>114,000</td>
<td>63,700</td>
<td>50,300</td>
<td>152,400</td>
</tr>
<tr>
<td>Pancreas</td>
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<td>55,500</td>
<td>48,800</td>
<td>152,400</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>96,900</td>
<td>61,200</td>
<td>35,700</td>
<td>171,800</td>
</tr>
<tr>
<td>Ovary</td>
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<td>75,700</td>
<td>125,200</td>
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<tr>
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<td>155,100</td>
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<tr>
<td>Kidney</td>
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<td>29,000</td>
<td>18,800</td>
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<tr>
<td>Corpus uteri</td>
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<td>41,165</td>
<td>144,900</td>
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<tr>
<td>Melanoma of skin</td>
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<td>7,900</td>
<td>7000</td>
<td>30,600</td>
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</table>
Table 3. Relative likelihood of death from specific types of cancer among specific age groups in less developed countries compared to developed countries. Raw data taken from IARC (16) and comparisons were performed using the GLOBOCAN Online Analysis - Age-Specific Tables tools, using Population as Less Developed or More Developed; Sex as Both Sexes, or Male or Female for sex-specific cancers (breast, cervix uteri, corpus uteri, prostate and testis); Data Type as Incidence or Mortality; and Statistic as Numbers.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Total</th>
<th>0-14</th>
<th>15-39</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-59</th>
<th>60-64</th>
<th>65-69</th>
<th>70-74</th>
<th>75+</th>
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<tr>
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<td>2.45</td>
<td>1.89</td>
<td>1.71</td>
<td>1.59</td>
<td>1.56</td>
<td>1.65</td>
<td>1.60</td>
<td>1.60</td>
<td>1.36</td>
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<td>1.95</td>
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<td>1.99</td>
<td>1.87</td>
<td>1.86</td>
<td>1.58</td>
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<td>1.05</td>
<td>1.08</td>
<td>1.03</td>
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<td>1.06</td>
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<td>1.10</td>
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which are well-established will be reviewed and their value to low- and middle-income countries discussed in the following section. Three cancers of importance in the developing world will be considered: lung, colorectal and breast cancer. These cancers share some similarity in the biochemical dysfunctions at their foundations, which will assist in rationalizing technical resources for genetic testing and analysis in developing world laboratories. Gastrointestinal stromal tumors, of special interest in Panama, will also be reviewed. Relatively simple genotyping tests which enhance risk assessment, prognosis or pharmaceutical choice in the management of these cancers will be referenced and their implementation in low- and middle-income countries will be evaluated. It should be noted that well-established options for personalized medicine for those cancers with higher relative morbidity and mortality in the developing world, such as lymphoma, multiple myeloma and cancers of the thyroid, prostate and testis are lacking at this time. Nonetheless, with the recent and complete sequencing of prostate cancers reported by Berger et al. (17), there are new insights into the molecular mechanisms giving rise to this group of cancers (18), the potential of targeting these pathways with new therapeutics (19) and of using their components as prognostic markers of clinical outcome, important in identifying men with aggressive forms of the disease who will benefit most from therapy (18, 20).

The third criterion is beyond the scope of this review, but rationalizes applications of personalized medicine that are sustainably affordable for developing world economies. The genetic tests used in personalized medicine and the chemo- and biologic therapies indicated by the results of these tests are expensive. Tests and therapies will either be strictly limited for specific cancers or patient groups, or innovative models of funding for personalized medicine will need to be developed.

**Lung and bronchial cancer** : Lung cancers are the leading cause of cancer death worldwide (Table 3; 16), with five-year survival rates of only 10% in most countries (21), a consequence of the advanced stage at which many are diagnosed (22). There is little difference in the likelihood of survival between patients in developed and developing nations (Table 3).

Lung cancers are classified morphologically according to the 2004 WHO scheme which identifies four major types: small-cell carcinoma, and the non-small cell carcinomas (NSCLCs), which are classified further into squamous cell carcinoma, large-cell carcinoma and adenocarcinoma, the predominant histological type in women and patients of Asian descent (21). NSCLCs comprise about 80% of lung cancers and patient age, gender and smoking history influence tumor histology (21, 23). Molecular classification confirms morphological classification and describes subtypes, especially for adenocarcinomas, although heterogeneity among the four major groups exists and cellular transitions between subtypes are observed, making absolute classification difficult (15, 24).

There are two well-defined applications of personalized medicine in managing lung cancer. The first application is genetic typing of $EGFR$ (also known as $Her1$ and $erb-b1$) in lung cancers to identify patients who will respond to tyrosine kinase inhibitors (TKIs), which act on $EGFR$, and which are demonstrated to prolong disease-free survival for some patients with advanced lung cancer.

$EGFR$ is a cell membrane receptor responsible for relaying, via phosphorylation cascades, gene activation signals which mobilize cells, progress cell cycle progression and angiogenesis. Several cancer types, including 43 to 83% of NSCLCs (25), show somatic $EGFR$ mutations which result in constitutive activation of the receptor, downstream phosphorylation events and uninhibited cell proliferation as a consequence.

Activating $EGFR$ mutations are observed in about 10% of all lung cancers. More than 18 mutations of phenotypic significance are found...
in the intracellular tyrosine kinase domain of the receptor involving exons 18 to 21, for which exon length ranges from 99bp (exon 19) to 186bp (exon 20) (26, 27, reviewed in 28). EGFR with activating mutations in these exons are sensitive to tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, both approved by the US FDA. These competitively bind to the ATP-binding cleft of the tyrosine kinase domain and their use significantly improves progression-free survival in patients with EGFR-mutant tumors, but not those with unmutated EGFR (29).

Genotyping of exons 18, 19 and 21 of EGFR in patients with advanced lung adenocarcinomas, especially patients who are non-smokers, women and those with Asian ancestry (27, 29-31), will identify patients sensitive to TKIs and may improve quality of life and survival among lung cancer sufferers in the developing world through the selective use of TKIs after the failure of standard first-line chemotherapies. This test will be especially useful in China, Japan and south-east Asia, and those low- and middle-incomes countries which have significant numbers of migrants from these regions, such as Panama (32).

The second application of personalized medicine to lung cancer management is the genotyping of EGFR and KRAS for mutations that predict the development of resistance to TKIs. In exon 20 of EGFR, the presence of the T790M substitution is associated with gefitinib resistance (33), and is a valuable predictor of patients who will show primary resistance to TKIs, as well as a molecular marker for patients formerly responsive to TKIs, but demonstrating therapeutic failure.

KRAS is one of the first GTPases in the phosphorylation cascade activated by EGFR. Activating mutations in KRAS codon 12 are observed in about 30% of NSCLCs (34) and most commonly in patients with a history of smoking (35). Activating mutations also observed in codon 13 and rarely in codons 59 and 61 (34, 36). Codon 12 and 13 mutations are associated with primary resistance to gefitinib and erlotinib (35), and as such, identify another group of patients who will not respond to TKIs.

Unfortunately, there is no reliable pre-symptomatic testing for lung cancer, which would significantly reduce the proportion of patients presenting with advanced cancers and increase the likelihood of survival through early detection and treatment. Similarly, genes with reliable prognostic value are limited: since 2001, a large number of studies have surveyed lung cancers for genetic markers which will predict disease outcome, refining the number from over 800 (15) to five (37). However, much debate remains about the utility of specific genetic markers, no clinical test is in routine use, and the application of such tests in resource-poor settings is some way off. Until reliable biomarkers for early detection and prognosis are identified, the best methods for preventing the development of advanced lung tumors will remain reduction of lung cancer risk factors through community education, and traditional radiographic screening for early-stage cancers. Nonetheless, value remains in genotyping lung cancer biopsies to assess sensitivity to TKIs.

Colorectal cancer: Colorectal cancers are one of the top five causes of cancer and cancer death worldwide (Table 2), and may arise sporadically or be caused by inherited mutations. Many begin with the mutational inactivation of the Adenomatous Polyposis Coli (APC) gene, a tumor suppressor which leads to dysregulated gene transcription, inactivation of other tumor suppressor genes and activation of proto-oncogenes (38). There is a small decrease in the likelihood of survival for patients with colorectal cancer in the developing world compared to developed countries (Table 3). Reliable applications for personalized medicine in the management of these cancers include pre-symptomatic risk assessment, diagnosis and tumor typing for drug selection.

Approximately 10% to 30% of all colon cancers occur with some heritable basis (39) and
mutations in a number of genes, including APC and others, are associated with familial colorectal cancer syndromes. Individuals and families at risk from heritable colon cancer may be identified with pre-symptomatic assessments following the US National Comprehensive Cancer Network guidelines for colorectal cancer screening, a document which could be adapted by countries of the developing world (40).

Pre-symptomatic and diagnostic tests for two of the most common heritable cancers of the colon are described below, Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP), together causing about 5% of all colorectal cancer. A number of other cancer syndromes with well-defined genetic foundations make a small contribution to the remaining 20-25% of colorectal cancers with familial bases, but the majority of this group is thought to be caused by low-penetrance, poorly-characterized susceptibility loci, for which genetic markers are currently unavailable (41). Personalized pre-symptomatic risk assessment and diagnosis in these cases is not yet possible.

HNPCC, also known as Lynch Syndrome, is an autosomal dominant disease, causing 2-4% of all colon cancers (39-42). No studies on the incidence and significance of HNPCC in Panama have been performed, although data from Colombia (43-45) and Mexico (46, 47) may be a useful basis for regional epidemiological studies. HNPCC manifests as colorectal carcinoma, endometrial carcinoma or cancers of the small intestine, ureter or renal pelvis and lifetime risk of developing colorectal cancer if diagnosed with HNPCC is 50-80% (41). To be assessed as having HNPCC, families should fulfill the Amsterdam I criteria, Amsterdam II criteria or Bethesda guidelines; the introduction of the two latter tests have increased the sensitivity of detection of families with HNPCC to above 50% (reviewed in 41).

The underlying genetic basis for HNPCC is reasonably clear: 70-90% of families show germline mutations in mismatch repair genes: MSH2 accounts for about 30-60% of cases, (41, 48); MLH1 accounts for about 30% of cases, (48); and MSH6 or PMS2 are largely responsible for the remainder (38, 40). Some debate remains about the importance of mutations in EXO1 (40, 49); PMS1 (40, 50); EpCAM, a gene directly upstream of MSH2 (41, 51) and MLH3 (40, 52), while up to 30% of HNPCC families have no genetic mutations detectable in the main mismatch repair genes described above (48). New and unique mutations in these genes continue to be reported from specific populations and those noted in Colombian patients (43-45) may be of particular interest in Panama. While genotypic studies have not yet been performed to confirm that genetic homogeneity exists between the populations of these countries, Panama and Colombia share common anthropological histories of colonization and settlement by European, African and Amerindian groups. We expect, therefore, that modest extrapolations of Colombian data may be relevant to Panama.

HNPCC families can be identified after assessment of an index case with colorectal cancer. Biopsied tissues are analyzed by immunohistochemistry for mutations in MLH1, MSH2, MSH6 and PSM2 (40). Tumor tissues can also be analyzed for microsatellite instability (MSI), which arises as a consequence of mutations in mismatch repair genes. Around 80-90% of colorectal cancers have MSI (40) and a panel of five microsatellites (BAT25, BAT26, D5S346, D2S123, D17S250) has been recommended for use in characterizing HNPCC tumors (38, 53). Sixty percent of HNPCC adenomas have high MSI (38), which is associated with a lower frequency of metastasis and better prognosis (54). It should be noted, however, that 10-15% of sporadic colorectal cancer also demonstrate MSI and positive MSI tests on tissue biopsies must be followed by pedigree analysis and genetic testing for mutations in mismatch repair genes before HNPCC can be defined (41, 42). If HNPCC is
suspected, genetic counseling and further testing is then recommended, according to guidelines, for the index case and asymptomatic family members (40).

FAP is another autosomal dominant disorder characterized by numerous adenomatous colorectal polyps with a tendency to form adenocarcinoma; penetrance by 40 years of age is almost complete (38, 55). Clinical variations on FAP include attenuated FAP, Gardner and Turcot syndromes, but all forms are associated with germline mutations in APC (55). FAP is responsible for less than 1% of colorectal cancer cases and 25-50% of FAP individuals will have \textit{de novo} APC mutations with no family history of the condition, with 20% of these patients also showing somatic mosaicism (38, 41). Nonetheless, there is value in the genetic screening of families of index cases as prophylactic endoscopic screening, initiated before 20 years of age, and prophylactic colectomy strongly reduces risk of colorectal cancer (38, 41).

APC is a gene of 160kb with up to 21 exons and many alternative transcripts (38, 56). Polakis \textit{et al.} (57) provides a summary of the somatic and germline mutations common in APC and a database of mutations and polymorphisms in APC is maintained by the International Society for Gastrointestinal Hereditary Tumours (58). (This database also tracks mutations and polymorphisms in HNPCC-associated genes.) Correlations exist between the location of these mutations in APC and the clinical presentation of FAP (55).

The second main application of personalized medicine in managing colon cancer is typing of colorectal tumors to improve therapeutic choice. A number of examples exist where genetic testing of tumors will guide drug use.

First-line chemotherapies for colon cancer include fluoropyrimidines (5-fluorouracil (5-FU) and capecitabine, the prodrug of 5-FU), oxaliplatin and irinotecan (59). 5-FU is metabolized by rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD) and a deficiency of this enzyme has been associated with severe 5-FU toxicity (60). The \textit{DPD} gene is well-characterized and a number of single-nucleotide polymorphisms (SNPs) have been associated with reduced DPD activity. Genetic screening of DPD before administering 5-FU to patients may be of value in avoiding toxicity and enabling more appropriate chemotherapeutic choices, although no regulatory steps dictate testing is yet mandatory (60, 61). A number of screening strategies for DPD mutations are available (62).

One biologic therapy for colon cancer targets EGFR, important in metastatic colon cancers, and also identified as significant in some lung cancers (above). Drugs which target EGFR in the treatment of colon cancer belong to a class of inhibitor acting against EGFR's extracellular domain. These inhibitors take the form of monoclonal antibodies which block the binding of EGFR's natural ligands, promote receptor internalization and degradation and prevent activation of downstream phosphorylation cascades (63). Monoclonal antibody products used in treating colon cancer include cetuximab and panitumumab, approved by the US FDA for use alone or in combination with other first-line chemotherapies (63, 64). The US FDA requires that all patients be tested immunohistochemically for EGFR expression before initiation of cetuximab and panitumumab therapy (65), although cetuximab has proven efficacious in colorectal cancer patients whose tumors do not express EGFR detectable by immunohistochemistry (66).

However, in a similar situation to that observed for lung cancers, colon cancers with \textit{KRAS} mutations in codons 12, 13 and rarely 61, show resistance to cetuximab and panitumumab (67-69). A Provisional Clinical Opinion from the American Society of Clinical Oncology (ASCO) therefore states that \textit{KRAS} genotyping should be another mandatory procedure before monoclonal antibody therapy can be prescribed.

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for colorectal cancer treatment (70); approximately 40% of patients who will not respond to cetuximab or panitumumab will have mutated KRAS (71).

Chemorefractory colon cancers may otherwise involve mutations in exon 15 of BRAF which encodes a protein acting downstream of KRAS (10% of resistance cases); PI-3K, encoding a protein kinase activated by EGFR as an alternative to KRAS (15-20% of resistance cases); and PTEN, whose product acts in the phosphorylation cascade downstream of PI-3K (25% of resistance cases) (reviewed in 71). A large body of data suggests screening of colorectal cancers for PI-3K and BRAF, as well as KRAS could better identify patients likely to benefit from monoclonal antibody therapy, but official statements from bodies such as ASCO have not yet been made regarding these tests. An US-FDA approved test for the resistance-conferring V600E mutation in BRAF is available, but currently only indicated for non-colorectal cancer (melanoma) (72). Clinicians should, however, consider BRAF, PI-3K or PTEN mutations in cases of cetuximab or panitumumab therapy failure.

Breast cancer: Breast cancer is one of the top five cancer killers in both the developed and developing worlds, and is the most significant sex-specific cancer in terms of morbidity and mortality (Table 2). Likelihood of death from breast cancer in the developing world is nearly twice as high as in the developed world for women aged 50 to 69, a possible consequence of the absence of mammography programs in these countries (Table 4; 73). Community-based education programs promoting and making available mammograms for women from specific demographic groups and regular breast checks are important in the early detection of breast cancers, but there are also applications of personalized medicine that could be used by the developing world, including pre-symptomatic risk assessment, prognosis, diagnosis and pharmacogenomic testing.

Up to 20% of breast cancers are hereditary (74) and about 40-60% of these are due to autosomal dominant gene mutations in the BRCA1 and BRCA2 tumor suppressor genes, which repair DNA or dictate to cells in which DNA cannot be repaired that the cell should undergo apoptosis (73, 74). Of the 80% of breast cancers arising sporadically and without family history, 5% will also show mutations in one of these genes (75): a total of 5-10% of all breast cancer patients will have mutated BRCA1 or BRCA2. Patients with these mutations have a 40-80% chance of developing breast cancer and analysis of these genes in families with a history of breast cancer is a valuable pre-cancer risk assessment tool (73, 76). Such families in the USA are being identified and genotyped using detailed guidelines on familial breast and ovarian cancer published by the National Comprehensive Cancer Network, a document similar to that for colorectal cancer screening, which could also be adopted by other countries (76). Identifying mutations in these genes is not only a risk assessment tool for families and individuals, but indicates that the patient may benefit from therapy with PARP inhibitors, particularly effective against breast cancers with mutated BRCA1 and, or, BRCA2 (77, 78).

Testing for mutations in a number of other high-penetrance genes associated with breast cancer is also of clinical value, and those genes include tumor suppressor genes TP53 and PTEN, and CDH1, respectively associated with Li-Fraumeni, Cowden and Hereditary Diffuse Gastric Cancer Syndromes, three hereditary conditions with an increased risk of breast cancer (73, 76). It should be noted that Li-Fraumeni Syndrome is also associated with increased risk of colorectal cancer (38) and that MLH1 and MSH2 mutations, associated with familial HNPCC colorectal cancer, are also implicated in hereditary breast cancer (73). A number of other, low- and moderate-penetrance genes which may contribute to breast cancer continue to be investigated and may be of clinical utility for pre-symptomatic risk assessment in the future (73).
Genetic profiling of tumors is the second major application of personalized medicine for breast cancer and assists in prognosis and choice of chemotherapies. Based on gene profiling, histology and immunohistochemistry, five subtypes of breast cancer have been identified and essentially distinguished by the expression of three genes: the *Estrogen Receptor (ER)* and *Progesterone Receptor (PR)*, two nuclear hormone receptors; and *HER2* (also known as *Neu* and *erb-b2*), an extracellular receptor and member of the EGFR family (reviewed in 73). HER2-like tumors over-express HER2; luminal A and luminal B types are ER-positive; basal-like tumors, also known as “triple negative” or “hormone unresponsive” tumors, are ER-negative, PR-negative and HER2-negative; and normal-like tumors resemble normal breast tissue (79). Luminal subtypes have best prognosis, while HER2-like and basal-like tumors have traditionally had poor prognosis (73). There is considerable variability in the incidence of subtypes observed among women of different racial backgrounds (73), which will be important for laboratories which serve patients of diverse racial backgrounds, as is the case in Panama, a country which has experienced migration waves from Europe, Africa, the Caribbean, North America and Asia. Testing continues on the sensitivity and specificity of two prognostic kits, available commercially, Oncotype Dx and MammaPrint, which profile 21 and 70 genes associated with breast cancer respectively, and which are designed to identify patients with higher likelihoods of relapse and the need for additional therapies (79).

Differences in prognostic outcomes are partly due to the roles that ER, HER2 and PR play, and how effectively they can be targeted by drugs. Patients with ER-positive tumors can be treated with drugs such as estradiol and tamoxifen, which lead to down-regulated HER2 expression. Patients with HER2-positive tumors can be targeted by trastuzumab, a monoclonal antibody which down-regulates cell proliferation, and lapatinib, a TKI acting on the tyrosine kinase domains of both HER2 and EGFR. Both therapies are US FDA approved. The use of both trastuzumab and lapatinib is strictly limited to patients with HER2-positive cancers, and the latter only for women on a regimen of complementary drugs. Immunohistochemistry and fluorescence *in situ* hybridization are two techniques used to assess HER2 expression on biopsy samples.

**Gastrointestinal stromal tumors**: Gastrointestinal stromal tumors (GISTs) are observed at a global incidence of 10-20 per million people each year and present as tumors of the stomach (50-60% of cases), small intestine (30%-40%), colon and rectum (5-10%) and esophagus (5%) (80) with a malignancy rate of 20-30% (81-83). Most GISTs arise as a consequence of somatic mutation, but familial GIST also exists with nearly 100% penetrance resulting in all affected family members manifesting multiple GISTs (reviewed in 84).

Biochemically, GISTs are associated with activating mutations in the *c-kit* and *pdgfra* genes, respectively encoding the KIT and PDGFRA oncoproteins, two membrane receptors with tyrosine kinase activity which are involved in cellular signaling pathways promoting cell growth and proliferation (85-91). Nearly 85% of GISTs express constitutively activated KIT and about 5% constitutively activated PDGFRA (92). Constitutive activation is associated with exon 11 in *c-kit*, and at a lesser incidence in exons 9, 13, 14 and 17, while activating mutations are most commonly associated with exons 12, 14 and 18 in *pdgfra* (84, 92). Familial GISTs most commonly arise from *c-kit* mutations in exons 8, 11, 13 and 17 and *pdgfra* mutations in exon 12 (84).

Imatinib is an US FDA-approved TKI used in the treatment of KIT-positive GISTs. Its clinical efficacy correlates with the specific *c-kit* or *pdgfra* mutation present, with *c-kit* exon 11 mutations responding most favorably (93). Immunohistochemistry for KIT expression and
genotyping GISTs for the c-kit and pdgfra mutations present are tools in determining the utility of imatinib for GIST patients.

However, resistance to imatinib occurs in 14% of the patients after 6 months of treatment and 50% of patients after 2 years of treatment (94, 95). Resistance mechanisms include the activation of alternative downstream signaling pathways, activation of other tyrosine kinase receptors, the loss of KIT expression and the development of secondary mutations in c-kit or pdgfra (96). Patients with treatment failure after initial success may demonstrate tumors which have developed second, activating mutations in exons 13, 14 and 17 of c-kit, or very rarely, in pdgfra (97). Therapeutic failure together with the presence of such secondary mutations allows identification of patients which may benefit from an alternative TKI therapy, sunitinib, which inhibits KIT, PDGFRA and the angiogenic vascular endothelial growth factor receptors (VEGFRs) (98).

Our group recently published one of few Latin American studies to evaluate the mutational status of the KIT/PDGFRA oncoproteins in clinical samples (99). We examined the histopathologic features of paraffin-embedded tumor tissues and the mutations in c-kit and pdgfra genes from 39 archived Panamanian cases, 1994-2004. The highest frequency of mutations was in exon 11 of the c-kit gene (70%), while mutations at a lower frequency were found in c-kit exon 9 and pdgfra exon 18. The results obtained in that study for c-kit and pdgfra validated our laboratory’s developing program of personalized mutational analysis, which also involves using EGFR and KRAS for lung and colon cancers, respectively.

**Applying personalized medicine for cancer in the developing world:** Cancers of importance in the developing world are those with high incidences of morbidity and mortality, those affecting young people and cancers for which survival rates are relatively lower. Three cancers with high incidence in low- and middle-income countries are lung, colorectal and breast cancers and in the previous section, applications of personalized medicine were examined for these. It was noted that these cancers not only share a similar significance for their impact on developing world patients, but similarity in the genetic mutations and biochemical dysfunctions that are at their basis.

These commonalities may guide diagnostic laboratories with limited resources to develop a concise portfolio of genetic tests that will provide maximum benefit for the greatest number of cancer patients, including:

1. **EGFR** genotyping of exons 18-20 for lung cancer patients, and immunohistochemical analysis of EGFR for colorectal cancer;
2. **KRAS** genotyping of codons 12 and 13 for lung and colorectal cancers;
3. **MSH2, MLH1 and APC** genotyping; microsatellite instability tests using BAT25, BAT26, DSS346, DSS123 and D17S250 markers; and immunohistochemical tests for MLH1, MSH2, MSH6 and PSM2 for colorectal cancer patients;
4. **BRCA1 and BRCA2** screening and **MSH2 and MLH1** genotyping for breast cancer patients and their families;
5. **HER2** immunohistochemistry or FISH analysis for breast cancer patients; and,
6. **KIT** immunohistochemistry and genotyping of c-kit (exons 9, 11, 13, 14 and 17) and pdgfra (exons 12, 14 and 18) for GIST patients.

In this section, the technical aspects of implementing such tests are briefly reviewed. A second group of tests for the genes **BRAF, PI-3K or PTEN, TP53 and CDH1** or their products could also be introduced, once standardized tests have been developed for these genes, and after the primary tests proposed above are established in laboratories. **EGFR testing:**Protocols for PCR and Sanger sequencing of EGFR for lung cancer patients from genomic DNA are available in the Developing world personalized cancer medicine.
supplementary material of Paez et al. (27) and Pao et al. (100). The relevant exons for lung tumor analysis, 18-20, are short, ranging from 99bp (exon 19) to 186bp (exon 20) (26, 27, reviewed in 28), and these protocols can be performed using standard PCR and sequencing equipment. More advanced techniques involving real-time PCR, high-resolution melting analyses and pyrosequencing are under development (36). Evidence of EGFR expression by immunohistochemistry of biopsy samples is requisite in the US before cetuximab and panitumumab therapy is prescribed for metastatic colorectal cancer (65). For this analysis, the Dako EGFR pharmDx® kit is recommended (65). Other anti-EGFR antibodies in common use for analysis of formalin-fixed, paraffin-embedded tissue are the CONFIRM™ anti-EGFR primary antibody and the 31G7 clone (101, 102).

KRAS testing: The assays described as appropriate for KRAS genotyping in ASCO’s Provisional Clinical Opinion on testing for mutations in codons 12 and 13, are real-time PCR and direct sequencing (70). A number of other techniques have been described to analyze KRAS (36, 103, 104), including one which claims to provide results on codon 12 testing in 60 minutes (105). There is no US FDA-approved test (70), but commercial testing kits are available (see below).

MSH2 and MLH1 testing: Several types of analysis are available for mutation testing in MSH2, MLH1 and the mismatch repair genes of lesser importance in their contribution to colorectal cancer, PMS2 and MSH6. The most common involve sequencing of the entire coding region and deletion/duplication analysis, while less common methods involve sequence analysis of select exons, mutation scanning of the entire coding region and targeted mutation analysis (106-109). Hampel et al. (110) review and compare several of these methods. Antibodies for immunohistochemistry for mutations in MLH1, MSH2, MSH6 and PSM2 are available commercially from a number of companies, as are kits genetic analyses of MLH1 and MSH2 (see below).

APC testing: A number of molecular tests are available for patients suspected of Familial Adenomatous Polyposis. APC mutations are most reliably detected by complete sequencing of exons and intron-exon boundaries, which has largely replaced the in vitro protein truncation test (55). Some laboratories in the US and elsewhere also offer sequence analysis of select exons, mutation scanning, targeted mutation analysis, linkage analysis and deletion/duplication analysis using Southern blot, multiplex ligation-dependent probe amplification and quantitative PCR (55, 111).

BRCA1 and BRCA2 screening: Cancer-associated mutations in BRCA1 and BRCA2 are distributed along the entire coding region and intronic sequences flanking each exon. Identifying such mutations requires examination of the entire gene sequences, a time-consuming and costly analysis, or the use of various scanning techniques, of which a number have been developed and reviewed for sensitivity and specificity, and whose use may be appropriate in diagnostic laboratories of some developing countries (112, 113). Recent advances in pyrosequencing also allow for deep-sequencing of an individual patient’s BRCA1 and BRCA2 genes with relative ease and speed. The development of mini-pyrosequencers costing less than 200,000 USD and commercially-prepared reagents for BRCA1/2 analysis may make routine sequencing for families and individuals at increased risk of breast cancer a possibility in middle- to mid-upper income countries.

An alternative approach is to analyze BRCA1 and BRCA2 for only specific mutations. In certain populations in the Philippines (114), Pakistan (115), Colombia (116) and other developed and developing nations, founding effects make certain BRCA1 or BRCA2 mutations more common than others and these may serve as particular targets for simplified

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genotyping tests for families of certain geographical or ethnic origins (112). Of interest to Panama are the mutations observed in high frequency in the Hispanic populations of Colombia, well as those observed among Afro-American women, as nearly 10% of Panama’s population identifies as being of African descent (117).

**HER2 testing:** Several US-FDA approved tests exist for analysis of HER2 expression in breast cancer biopsies, demonstration of which is a necessary step before women can be prescribed trastuzumab or lapatinib. These tests are based on detection of the HER2 protein or quantification of HER2 gene copy number and include the Dako Anti-HER2 IHC System (the Hercep Test) and the Ventana Medical Systems Inform Dual ISH test.

**KIT testing and c-kit and pdgfra genotyping:** Somatic mutations in exons 9, 11, 13 and 17 of c-kit can be evaluated using PCR-based assays and direct cycle sequencing of the PCR product. Patient samples with non-mutated c-kit can then be evaluated for pdgfra gene mutations in exons 12 and 18 (97, 118). Immunohistochemistry for KIT expression can be performed using the DakoCytomation c-Kit pharmDx™ product (US-FDA approved) and other commercially available anti-KIT monoclonal antibodies.

**Commercial kits:** Several companies offer products for genetic analysis and pyrosequencing, the major ones being QIAGEN (genetic analysis for KRAS, EGFR, BRAF, PIK3CA and others, and pyrosequencing for BRAF, KRAS and EGFR) and Roche Molecular Diagnostics (genetic analysis for KRAS, EGFR and BRAF). Wang et al. (119) review several commercial products for KRAS mutation testing and note the importance of identifying a gold-standard assay to determine reference standards. MLC Holland sells multiplex ligation-dependent probe amplification kits for BRCA1, BRCA2, CHD1, PTEN, MLH1, MSH2, APC, MSH6 and DPD analysis. The SNaPshot(R) Multiplex System from Applied Biosystems has been applied for SNP analysis of MLH1 and MSH2 (120) and KRAS mutations in codons 12 and 13 (103).

**Other resources:** The National Center for Biotechnology Information (NCBI) hosts a useful database called GeneTests (http://www.ncbi.nlm.nih.gov/sites/GeneTests/). Its main feature is the listing of tests offered in the USA and globally for a large number of genetic disorders. It is organized by genetic disorder and describes laboratories which offer testing and the method of testing employed, if a variety of protocols are available. It can be searched by disease or gene name and also has links to GeneReviews, which are peer-reviewed descriptions of genetic diseases.

**Conclusion**
Cancer has overtaken infectious disease as the leading cause of death in the developing world. Of significance are lung/bronchial, liver, stomach, esophageal, colorectal, breast and cervical cancers in adults, and leukemia, Non-Hodgkin lymphoma, brain and nervous system cancers, kidney cancer and Hodgkin lymphoma in children (16), with the likelihood of surviving cancer being decreased for the developing world for Hodgkin and non-Hodgkin lymphoma; multiple myeloma; thyroid, prostate and testicular cancer, or if you are less than 14 years of age.

Many low- and middle-income countries lack even basic resources for diagnosing and treating cancer, but others with better developed medical and scientific infrastructure, such as Panama in Central America, are beginning to apply personalized medicine for pre-symptomatic risk assessment, diagnosis, prognosis and treatment of solid tumors and lymphoproliferative malignancies. In Figure 1, we list a number of initiatives to expand the existing program of personalized medicine in that country.

Even in regions with better scientific and medical resources, however, the application of personalized medicine for cancer is being...
balanced against other health concerns and prioritized for cancers that affect the largest numbers of people, the young, or those for which there is a significant relative decrease in life expectancy compared to wealthier nations. In this review, we propose newly developing diagnostic laboratories focus initially on a group of cancers which have common biochemical dysfunctions at their origins, and the development of a small portfolio of tests, based on hereditary cancers with high-penetration genes and biomarkers which have high value to physicians making treatment choices.

In both resource-rich and resource-poor settings, the clinical use of personalized medicine cannot occur without building the necessary technical, legislative, administrative and human infrastructure, (Figure 2). Most developing countries will have to establish, expand or strengthen this infrastructure, a process which will involve cooperation among many different groups. Even in medically and scientifically advanced nations, there are considerable challenges to translating basic cellular and molecular research to effective patient care for personalized medicine in cancer (121) and the developing world has the opportunity to learn from what is emerging in other places, or to create new solutions that serve their local community best.

Finally, the utility of certain tests and therapies for cancer care is unquestioned, but concerns about the processes validating others still remain (122). As Offit (7) comments, patients

**Fig. 1. Priorities for establishing personalized oncology care in Panama**

<table>
<thead>
<tr>
<th>1.</th>
<th>Implement technologies and tests described in this review:</th>
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<tr>
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<td>Identify funding for their implementation</td>
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<td>Optimize tests by conducting retrospective epidemiological surveys using archived tissues of colorectal, lung and breast tumors to analyze the types and incidence of specific genetic mutations, and from these and patient case files, infer the historical prevalence of familial cancer syndromes in Panama;</td>
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<td>Offer and perform genetic analyses for patients with cancer of the lung, colorectum, breast and GIST, and their families, to aid physicians in therapeutic choices and to identify families with hereditary cancer risk;</td>
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<td>2.</td>
<td>Develop clinical infrastructure to match and respond to new genetic technologies available:</td>
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<td>Educational resources for oncologists and allied health professionals;</td>
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<td>Participation from peak medical bodies to support new initiatives in personalized medicine;</td>
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<td>Funding for routine screening programs, including endoscopy and mammography, for families identified as having hereditary colorectal or breast cancer syndromes;</td>
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<td>Funding and legalization of chemotherapies indicated by genetic analyses;</td>
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<td>3.</td>
<td>Develop post-graduate degree programs in genetic counseling, medical genetics, molecular medicine and biotechnology;</td>
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<td>4.</td>
<td>Publication education:</td>
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<td>Improve participation in cancer prevention and screening programs by promoting HPV and HBV vaccines, Pap smears, mammography, prostate cancer screening, lung cancer screening, and lifestyles which include healthy diets, exercise, responsible alcohol consumption and smoking reduction;</td>
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<td>Improve genetic literacy in schools and through public education programs.</td>
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and their families must be protected from premature translation of research findings. The inequities in health care experienced by resource-poor nations should not be addressed by transforming them into testing grounds for new personalized therapies and tests, but by ensuring that legal, financial, technical and medical barriers are lowered to allow transfer and uptake of the best technologies available elsewhere.

The lowering of these barriers will take considerable cooperation, but is vital for the success of programs of personalized medicine in the developing world. The tests and therapies discussed in this review are costly, which limits their availability even to patients of relative affluence (121). Making them available to the developing world will require innovative models of funding, possibly along the lines of the International Finance Facility for Immunisation’s vaccine bonds, and will require considerable negotiation, financial support and good will from drug manufacturers, international health agencies, philanthropic organizations and national governments.

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