

# Pragmatic medicine in solid cancer: a translational alternative to precision medicine

Jan Brábek<sup>1</sup>  
Daniel Rosel<sup>1</sup>  
Michael Fernandes<sup>2</sup>

<sup>1</sup>Department of Cell Biology, Faculty of Science, Charles University in Prague, Prague 2, Czech Republic;

<sup>2</sup>Medbase, Chapel Hill, NC, USA

**Abstract:** The precision medicine (PM) initiative is a response to the dismal outlook in solid cancer. Despite heterogeneity, common mechanistic denominators may exist across the spectrum of solid cancer. A shift from conventional research and development (R&D) toward PM will require conceptual and structural change. As individuals and as a society, we welcome innovation, but question change. We ask: In solid cancer, does PM identify and address the causes of prior failures, and, if so, are the proposed solutions feasible? And, when may we expect safer, more effective and affordable drugs in the clinic? Considerations that prompt a pragmatic rethink include a failure analysis of translational R&D in solid cancer suggesting that trials and regulations need to be aligned with the natural history of the disease. In successful therapeutic interventions in chronic, complex disease, surrogate markers and endpoints should be consistent with the Prentice's criteria. In solid cancer, drug induced tumor shrinkage, is a drug effect and not a disease response; tumor shrinkage does not reflect nor predict interruption of the disease. Overall, we support a pragmatic, multidisciplinary, and collaborative R&D, and suggest that direction be set by clinical need and utility, and by questions, not answers. PM will prove worthwhile if it could improve clinical outcomes. The lag in therapeutics relative to diagnostics is a cause for confusion. Overdiagnosis adds to fear and harm, especially in the absence of effective interventions. A revised initiative that prioritizes metastasis research could replicate the successful HIV/AIDS model in solid cancer. A pragmatic approach may further translational efforts toward meaningfully effective, generally available, and affordable solutions.

**Keywords:** precision medicine, pragmatism, solid cancer, translation, metastasis, RECIST, 21st Century Cures Act, Paul Ehrlich

## Introduction

### “What is the question?”

In scientific programs, especially one with health care and economic implications, questions usually precede answers.<sup>1</sup> The precision medicine (PM) initiative lists several solutions, but the questions remain elusive. In the context of remarkable successes of the pharmaceutical industry in combating serious and widespread acute and chronic diseases, the question is: why are effective and affordable therapies still not available for solid cancer? In the absence of effective and affordable therapies, the value of national screening programs is questionable, and there is a concern that diagnostics may outpace therapeutics. In an earlier era, there were no medicines for serious diseases such as solid cancer. Today, curative medicines exist, but are unaffordable for the large majority of patients. In the treatment of solid cancer, we have progressed from the incurable to the unaffordable (Figure 1).

Here, we make the case for a shift in research and development (R&D) focus to relevant clinical outcomes, antimetastasis, and away from tumor shrinkage.<sup>2</sup> Tumor

Correspondence: Jan Brábek  
Department of Cell Biology,  
Faculty of Science, Charles University  
in Prague, Vinicna 7, 12843 Prague 2,  
Czech Republic  
Email brabek@natur.cuni.cz



**Figure 1** "You've got something unaffordable".

**Note:** Courtesy of Banx Cartoons/Financial Times, Thursday September 24, 2015, page 12, with permission.

shrinkage does not qualify as a surrogate marker of efficacy relative to the natural history of the disease. A focus on antimetastatic interventions may not only be appropriate to the natural history of solid cancer, but will also justify earlier diagnosis via meaningful population screening.

## Precision medicine

The PM initiative is a major component of the 21st Century Cures Act, which, in part, is structured to accelerate the discovery, development, and delivery of useful drugs.<sup>3,4</sup> PM is a modest proposal with two components: a focus on cancer and the development of precisely targeted drugs, and a longitudinal study of at least 1 million people to explore genetic and environmental determinants of health and disease.<sup>5,6</sup> With the current and increasing concern on affordable medicines, especially in cancer, it is commendable that this initiative was prompted and levered by a significant reduction in the price of genome sequencing.<sup>7</sup> If the lower cost of goods translates to lower drug prices, then the PM initiative could be an ideal "fit" with the Affordable Care Act.<sup>8</sup>

The response to the PM initiative has been mixed (Table 1).<sup>7,9–16</sup> The bias toward genomics at the expense of the environment, and on the individual at the expense of the population needs to be clarified. It is difficult to target an intervention to both individuals and populations simultaneously. The role of the environment in disease and the

**Table 1** Joyner and Paneth pose seven questions for PM

1. Does the human genome contribute to disease risk prediction?
2. Will gene-based drug targeting and development fulfill its promise?
3. What will electronic medical records contribute?
4. What kinds of studies should be mounted in personalized medicine?
5. How should institutional conflicts of interest be managed in personalized medicine?
6. How will personalized medicine affect the costs of medical care?
7. Where is the public health benefit?

**Note:** Data from Joyner and Paneth.<sup>16</sup>

**Abbreviation:** PM, precision medicine.

therapeutic decision to target sick individuals or populations have been debated for decades.<sup>17,18</sup> Today, we realize that genetic and environmental factors, within the context of disease, are distinct entities, and that, though connected, are inseparable.<sup>19</sup> Will the focus on genomics underestimate the role of the environment in gene–environment interaction research?

To strategize a rational response to disease, problems need to be precisely defined before precise solutions are presented. The history of medicine indicates that a better understanding of epidemiology and pathogenesis precedes diagnostic and therapeutic advances; following Kuhn,<sup>20</sup> "failures, not successes have been the driving force behind innovation". The earlier experience with antibiotics in combating infection was a huge success, but today, science is driven toward overcoming failure in combating drug resistance. The analogy to the treatment of solid cancer is evident – the challenge is toward the development of meaningfully effective drugs at affordable prices.<sup>2</sup>

Relative to solid cancer, we ask:

- Is our method for the clinical evaluation of targeted anticancer drugs (response evaluation criteria in solid tumors, RECIST) consistent with the natural history of solid cancer?
- Is intratumoral heterogeneity a conceptual or operational obstacle to a precision approach in medicinal chemistry?
- Why do precisely targeted drugs invite resistance?
- Why, commensurate to its relevance, is dedicated antimetastasis research neither recognized nor funded?

In contrast to Jameson and Longo,<sup>13</sup> a careful and conceptual analysis of needs may be more relevant to the justification of the PM initiative than answers to unasked questions – why are we continuing to overpromise and underdeliver in the treatment of solid cancer?<sup>21</sup>

In the context of serial failures in drug development in solid cancer, nonmeaningful improvements in efficacy, the almost predictable development of drug resistance, and

astronomical pricing,<sup>22–24</sup> a novel rethink of the R&D and business models is appropriate and timely. High prices do not always reflect the costs of innovation; they are necessary to cover the loss from failures in late-phase trials and recalls following market authorization.<sup>24</sup> High drug prices are not universal; they are especially evident in free-market economies where the optimal price is what the market can bear.

The immediate need is an expansion of cancer care and control, especially in low- and middle-income countries.<sup>25</sup> A reduction in clinical trial failures may lower the price of goods and allow for effective, accessible, and affordable medicines for all.<sup>2</sup> Complexity of cancer and the costs of drug development are weak excuses for failure. We succeeded with an equally if not more complex disease, which was an epidemic, communicable, characterized by rapid mutations, and a fatal course – HIV/AIDS.<sup>26–28</sup> Edmondson<sup>29</sup> explains that in business and public policy, learning from failures is a sound principle for strategy formulation. A failure analysis suggests that a directional rethink – trial end points and regulations – and an emphasis on antimetastasis drug development are high on the list of immediate needs.

A shift in approach toward a precision-based and personalized frame – from the phenotype to the genotype – will require major structural changes in medicine and therapeutics. However, a larger policy question lurks in the background: Will these initiatives presage a personalized and private medicine framework for all (oxymoron intended), and the imminent demise of public health?<sup>30,31</sup> The premise of PM – prevention and treatment in the individual – may be at odds with public health strategy in that population-wide interventions are much more effective in reducing the incidence of disease than interventions in high-risk individuals.<sup>18,30,31</sup>

## Clinical trials

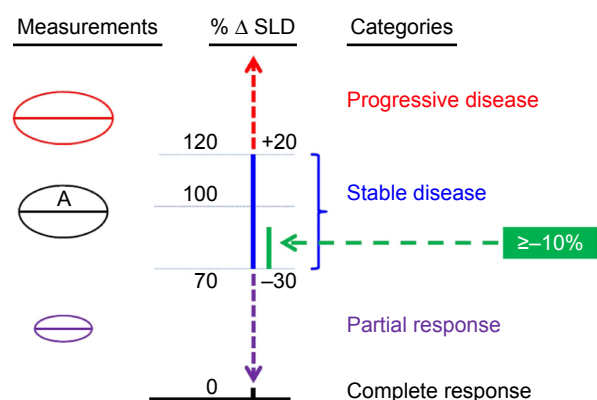
Burton et al<sup>32</sup> define genetic epidemiology as a discipline closely allied to traditional epidemiology that focuses on the familial, and in particular genetic, determinants of disease and the joint effects of genes and nongenetic determinants. Crucially, appropriate account is taken of the biology that underlies the action of genes and the known mechanisms of inheritance.<sup>32</sup> Accordingly, novel elements of clinical trial design will likely include the development and validation of prognostic and predictive biomarkers and classifiers, novel trial designs,<sup>33</sup> and a prospective plan of analysis.<sup>34</sup> This is important because clinical trials are the foundation upon which PM will be evaluated and implemented in individuals and populations.

The transition from conventional practice to PM will be neither simple nor easy. Problems have been identified and solutions have been proposed.<sup>9,13,35–39</sup> Specifically, the European Society of Medical Oncology has published a comprehensive position paper detailing the promises and challenges in the delivery of PM in oncology.<sup>39</sup> In brief, PM requires specialized centers to provide guidance, precise and standardized genotyping, and appropriate management of patients in trials and in the clinic. In this context, Booth and Tannock<sup>40</sup> propose that a few well-executed clinical trials performed at centers of excellence can complement population-based observational studies to expedite the evaluation of novel interventions. This proposal receives support from Kocher and Roberts<sup>41</sup> who state that the most expensive step in creating a new drug is conducting clinical trials, and that high-frequency, material information on clinical efficacy and safety comes from the first few hundred patients studied in a trial. Accordingly, large trials that add unwanted noise into the system may not be necessary. In fact, N-of-1 clinical trials, for biomarker studies rather clinical end points, may represent an efficient format for PM.<sup>42–44</sup>

## Regulations

Contrary to received wisdom, advances in science rarely extrapolate passively and painlessly to the approval of new drugs – regulations define and allow for the efficacy profile of products destined to the market. It is self-evident that translation to PMs requires precision regulations.

For too long, drug approval in solid cancer has been based on the RECIST convention, namely, tumor shrinkage<sup>45,46</sup> (Figure 2). This is the case despite the near-universal recognition that the tumor shrinkage end point is a relic of the cytotoxic era and far from a precision end point.<sup>47</sup> For targeted drugs, RECIST may not be fit for purpose.<sup>48–50</sup> “Progressive disease”, as defined by RECIST, is an increase in size, not progression of the disease. The latter is defined by continuing local invasion and metastasis. And again, “response”, as defined by RECIST, is a decrease in tumor size, but this is unrelated to inhibition of invasion or of the metastatic process. A complete response, disappearance of all lesions, is rarely seen. We maintain that tumor shrinkage is a treatment effect, and not a disease response. In a commentary in *J Natl Cancer Inst*, Oxnard et al<sup>51</sup> make our point, but in a confusing manner. Their title reads: When progressive disease does not mean treatment failure: reconsidering the criteria for progression. They state that the RECIST progression criteria were not developed as a surrogate for survival, and this makes interpretation of a “response” difficult. Their



**Figure 2** Precision science meets imprecise regulations.

**Notes:** The RECIST scheme relates to changes in tumor size.<sup>49,50</sup> It is a categorical classification based on the longest diameters of tumor images. The categories are arbitrary and wide. The stable disease category spans a change of  $-29\%$  to  $+19\%$ . Recently, a 10% or greater decrease in tumor size has been proposed as a cutoff limit to declare response for targeted drugs, mainly angiogenesis inhibitors.<sup>51,52</sup> 'A' refers to the longest diameter of tumor in one dimension.

**Abbreviations:** %  $\Delta$  SLD, percent change in sum of longest diameters of target lesions; RECIST, response evaluation criteria in solid tumors.

likely point is that a RECIST-based increase in tumor size does not imply treatment failure. We agree, and ask: in that case, why should a RECIST-based tumor shrinkage signify treatment success?

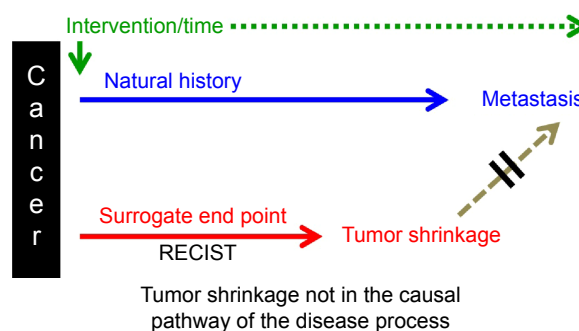
Krajewski et al<sup>52</sup> at the Dana-Farber Cancer Institute report that a 10% or greater shrinkage in tumor diameter in the first follow-up scan predicts clinical outcome in patients with metastatic renal cell carcinoma treated with angiogenesis inhibitors (Figure 2). On the basis of this study, and a survey of the literature, Chen et al<sup>53</sup> at the National Cancer Institute (NCI) support a 10% rule for declaring a response to noncytotoxic drugs. If confirmed, the implications to oncologists are substantial; the stable disease category will now be partitioned into a responsive subcategory (tumor size change from  $-10\%$  to  $-19\%$ , and merge with partial response) and a nonresponse subcategory (change from  $-9\%$  to  $+29\%$ , and merge with progressive disease). This modification will result in three categories: progressive disease, partial response, and complete response.

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Returning to conventional RECIST, the appearance of a new lesion (metastasis) indicates progressive disease.<sup>45,46</sup> But with protocol constraints to focus on selected target lesions, new metastases may be overlooked, especially if

the primary tumor shows marked shrinkage; the desired and publicized end point is tumor shrinkage. Therefore, it may be advisable to programmatically examine organs and sites of metastatic predilection (nontargets) for new lesions. Clearly, the appearance of a new metastasis on treatment indicates that the drug is ineffective. Today, radiology is faced with the challenge of evaluating changes during therapy quantitatively and of visualizing therapeutic effects that are more discrete (eg, necrosis, altered tumor perfusion). Höink et al<sup>54</sup> have recently addressed innovative developments and requirements for radiology across the spectrum of solid cancer.

In Greek mythology, Procrustes either stretched or cut his guests to make them fit the bed. Today, cancer clinical trials recapitulate a Procrustean scenario: precisely targeted drugs are being resized on a RECIST bed, and the dismal outcome is predestined.<sup>55</sup> Novel biomarkers and advanced imaging that track drug response in the context of the natural history of solid cancer (not just tumor shrinkage) are essential to further the oncologic objectives of PM.<sup>56-61</sup> Validity of a biomarker is established by authenticating its correlation with clinical, not regulatory outcomes based on tumor shrinkage.<sup>62</sup> It stands to reason that existing and investigational biomarkers, identified by mining clinical trial data based on RECIST (tumor shrinkage) and "validated" by regulatory decisions, may not be useful. If the aim of PMs is to prevent progression of the disease, then we need biomarkers of local invasion and the propensity to metastasis. Following Aronson,<sup>63</sup> the chain of events in a disease process linking pathogenesis to outcome is fragile, and the better we understand the nature of the path a disease takes and the pharmacology of a drug that affects it, the better biomarkers we will be able to develop in diagnosing, staging, and monitoring disease and its response to therapy. Accordingly, it may be best that drug and biomarker development and the selection of surrogate end points for clinical trials are aligned with the natural history of the disease<sup>64</sup> (Figure 3).



**Figure 3** Tumor shrinkage is a treatment effect and not a disease response.

**Note:** For a surrogate end point to be an effective substitute for clinical outcome, effects of the intervention on the surrogate must reliably predict the clinical outcome.

**Abbreviation:** RECIST, response evaluation criteria in solid tumors.



The Prentice criteria are a set of conditions that specify the conditional independence of the impact of treatment on the true end point, given the surrogate end point. In brief, the surrogate end point must be correlated with the clinical outcome and must fully capture the net effect of treatment on the clinical outcome.<sup>65</sup> It is widely accepted that this set of criteria ensures the validity of a surrogate end point (Figure 3).

However, Berger<sup>66</sup> disputes this claim and points out that these criteria alone ensure that an observed effect of the treatment on the true end point implies a treatment effect also on the surrogate end point, but contrary to popular belief, it does not ensure the converse, specifically, that the observation of a treatment effect on the surrogate end point can be used to infer a treatment effect on the true end point.

Failures in development may logically be attributed to a mismatch between precision science and imprecise regulations.<sup>47,67</sup> The need for a regulatory rethink has been both anticipated and covered by Collins and Varmus:<sup>3</sup> “achieving the goals of precision medicine will also require advancing the nation’s regulatory framework”. In solid cancer, we support a closer fit between related science (epidemiology, cell biology, pharmacology, and medicinal chemistry) and clinical trials, and also an agreement on novel translational end points that reflect a meaningful interruption in the progression of the disease, not just tumor shrinkage (Figure 4). Although translation is important, funding should not be at the expense of the related and contextual nonclinical and preclinical sciences. Otherwise, there may be little to translate!<sup>68</sup>

Despite the dismal consequences of the RECIST regime, even today, authors continue to emphasize that end points

need to reflect benefit to patients, but advise that changes in tumor size either in absolute terms (response and progression) or relative to control (progression) are clinically relevant.<sup>69</sup>

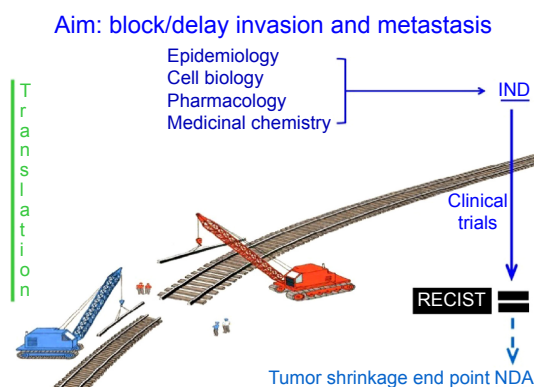
## Metastasis

On average, approximately 5% of total cancer research funding is spent on investigating metastases in Europe, and most likely in the USA and Japan, yet metastatic disease is the direct or indirect cause of over 90% of all cancer deaths.<sup>70</sup>

In 2007, in a landmark publication, Eccles and Welch<sup>71</sup> stated the obvious: “the prevention and/or elimination of spread of the disease, will represent the most important improvement in morbidity and mortality”. Today, patients fear the “M” word more than the “C” word,<sup>70</sup> and it is surprising that the “M” word does not appear in PM manifesto.<sup>3</sup> Oncologists ask: why does cancer therapy lack effective antimetastasis drugs?<sup>72</sup> And pharma scientists bemoan the lack of regulatory guidances for antimetastatic drugs.<sup>73</sup> This is the case despite the large and growing backlog of possibly antimetastatic drug candidates in the pipeline.<sup>74</sup> In solid cancer, precision science, related to local invasion and metastasis, has been long practiced by cell biologists and medicinal chemists.<sup>75–86</sup> Interestingly, the cell-migration-related signaling machinery is similar in both normal development as well as in invasion and metastasis.<sup>82,86</sup> This could represent a problem, or an opportunity, for antimetastatic drug discovery. In our opinion, the shift in discovery focus from the cancer cell alone and toward the tumor stroma is both a promising and pragmatic one.<sup>47</sup> Steeg et al,<sup>87</sup> in an open letter to regulatory agencies, suggested that preclinical drug development must consider the impact on metastasis. This is good advice, but the message, perhaps, would be best delivered to clinical oncologists.

In 2016, a major and unanswered question related to metastasis is the timing of dissemination – early or late, and whether the mechanisms act in parallel or sequentially.<sup>88–90</sup> Would precise treatment of the primary tumor cover that of the metastases? The parallel and independent evolution model proposed by Schmidt-Kittler et al<sup>88</sup> suggests that therapies that target properties of advanced primary tumors may be ineffective against metastatic cells that evolved independently after early separation from the primary tumor<sup>89</sup> (Figure 5). Gray<sup>90</sup> expands on the possible consequences of sequential or parallel progression of metastasis (Figure 6).

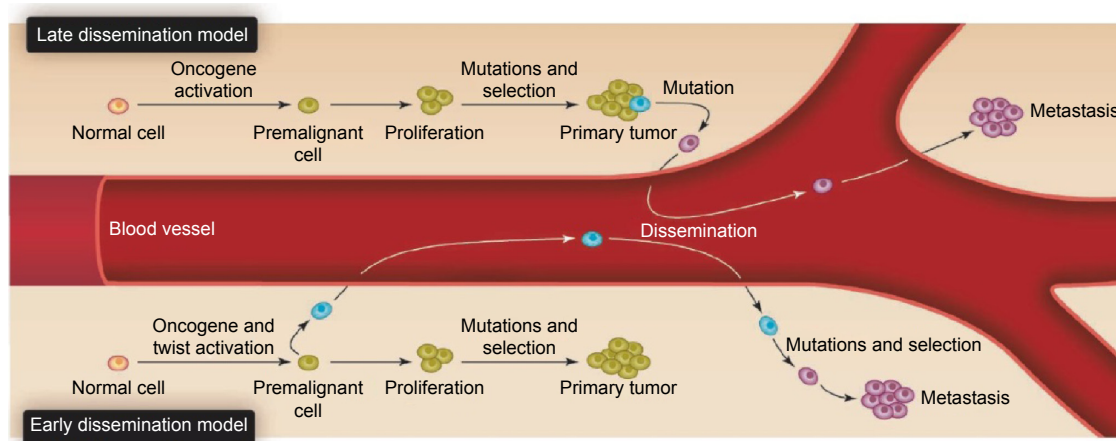
Often, the first question addressed to academic scientists submitting a translational proposal is: What are the chances of clinical benefit? On the other hand, the first question posed to pharma scientists proposing an anticancer drug



**Figure 4** Translational misalignment between PM and current regulations.

**Notes:** The product of mechanistic preclinical studies is evaluated by tumor shrinkage. Tumor shrinkage, as assessed in clinical trials, does not reflect nor predict a delay in local invasion or metastasis. The dismal clinical outcomes in solid cancer may be explained by the lack of precision regulations.

**Abbreviations:** IND, investigational new drug; NDA, new drug application; RECIST, response evaluation criteria in solid tumors; PM, precision medicine.



**Figure 5** The metastatic cascade – the evolution of malignancy.

**Notes:** Top – The late metastasis model (sequential progression) places the selection of genetic and epigenetic alterations inside the primary cancer. This implies that most properties of the primary cancer will be found in metastatic cells, which can be used as a surrogate marker for drug selection. Bottom – In contrast, in the early metastasis model (parallel progression), premalignant cancer cells accumulate at distant sites and may diverge genetically from the primary cancer. Consequently, they may not respond to drugs directed to the primary cancer. This consideration is also relevant to cancer dormancy. From Klein CA. The metastatic cascade. *Science*, 2008;321(5897):1785–1787.<sup>89</sup> Reprinted with permission from AAAS.

candidate directed to metastasis is: Is there a clear regulatory pathway? The usual and honest answer is: no, our drug inhibits invasion and may delay metastasis, but it does not cause tumor shrinkage. Accordingly, promising antimetastatic drug candidates are not advanced to the clinic and may explain, in part, the backlog noted earlier.<sup>91</sup> This interaction reflects the dichotomous and tragic outcome in cancer R&D: cell biologists and medicinal chemists advance knowledge on the mechanisms of invasion and metastasis, while pharma, oncologists, and regulators are locked in the tumor-shrinkage box. The former suffer from a lack of funds, while the latter

face clinical trial failures. But both camps, and especially patients and society, are the losers.

## Issues

Before proceeding further, a summary may be in order. Mechanisms fundamental to solid cancer are clearly differentiated from that of hematologic cancer and benign tumors.<sup>92</sup> Hematologic cancer is predominantly a disorder of clonal cell proliferation,<sup>93</sup> while solid cancer is primarily a disease of cell migration, invasion across the basement membrane into normal adjacent tissue,<sup>92,94</sup> and distant spread, termed metastasis.

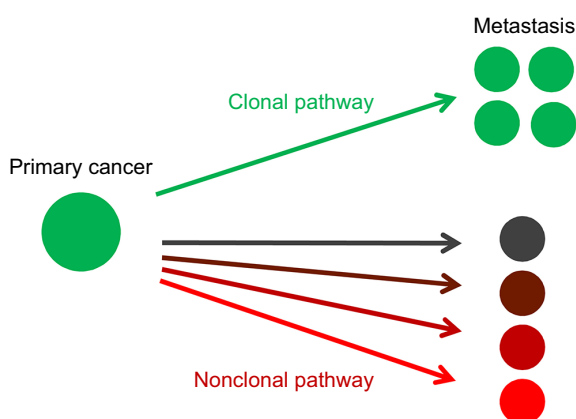
In addition:

- an increase in tumor size bears no direct relationship to the timing or intensity of metastasis,
- treatment-induced tumor shrinkage is, by definition a treatment response, not a disease response, and
- metastasis is the direct or indirect cause of over 90% of morbidity and mortality.

The clinical challenge is earlier detection of curable disease, and this implies both enlightened screening and the availability of antimetastatic therapies.

Here, the central question is: which failures in the current practice medicine and public health will genomic medicine address? Based primarily on the teaching of Rose,<sup>18,95</sup> we list seven concerns:

- 1) Unifying molecular biology and medicine at the bench and at the bedside
- 2) Genomics-driven oncology: framework for an emerging paradigm?



**Figure 6** Cancer progression models.

**Notes:** Clinical progression of solid cancer is by metastasis, not by an increase in size. Top – Clonal model. Properties of the primary cancer are retained in metastatic lesions. Bottom – Nonclonal model. Properties of the metastatic lesion differ from that of the primary cancer. In the clonal model, precision therapy, based on mechanistic characterization of the primary cancer, will apply to metastatic lesions. Such precision therapy is, however, not applicable for nonclonal model.

- 3) PMs and drug resistance
- 4) Earlier detection of disease and its consequences
- 5) Genes and the environment
- 6) 21st Century Cures Act
- 7) Program costs.

## Unifying molecular biology and medicine at the bench and at the bedside

Bridging the gap between the bench and the bedside is not easy, and Bates et al<sup>96</sup> at the NCI explain that 1) not every altered protein or pathway is a valid anticancer target; 2) drugs must effectively engage the target; 3) the biology of the systems we use must be well understood; and 4) clinical trials must be designed to assess whether the drug reached and impaired the target.

Discoveries from genome-wide association studies may improve the prediction of common diseases, but the question is whether this improvement is sufficient to enable PM? Janssen and van Duijn<sup>15</sup> argue that new gene discoveries may not improve the prediction of common diseases to a degree that it will change the management of individuals at increased risk. Improvements may only be expected if we manage to understand the complete causal mechanisms of common diseases to a similar extent as we understand those of monogenic disorders. Furthermore, although genomics research will make a major contribution to this understanding, the complexity of complex diseases may ultimately limit accurate prediction of disease in asymptomatic individuals, as unraveling their complete causal pathways may be impossible. Precision oncology is quite different from accurate oncology.

In disease, all risk factors are not created equal. The PM initiative, as presented, may give the impression that genomic considerations are more equal than traditional risk factors that have been epidemiologically validated. Horwitz et al<sup>97</sup> wonder whether an overreliance on technology for solutions may undermine clinical and environmental sciences resulting in depersonalized medicine? Further, to maximize the potential of the PM initiative, a new taxonomy of solid cancer based on genomics will be needed. Clinicians need not fear a genomic taxonomy – yet; medicine is already personalized. It is the phenotype that walks into your clinic, is grateful for your care and kindness, and pays your bill.<sup>98</sup>

## Genomics-driven oncology: framework for an emerging paradigm?

In an overview on precision oncology, Garraway et al<sup>99</sup> present a comprehensive and systematic assessment of cancer

genomic information and its accelerating clinical impact. This framework is based on the assumption that cancers are driven by genomic alterations that dysregulate oncogenic pathways, regulating cell growth and survival.<sup>100</sup>

In brief, implementation of this scheme requires:

- 1) characterization of the tumor genome,
- 2) filtration of genomic data through a knowledge base of US Food and Drug Administration (FDA) approved and investigational anticancer drugs, and
- 3) presentation of an annotated drug list to the treating oncologist that can be incorporated into clinical decision making.

However, this framework fails to describe the genomic connection to the key clinical outcome in solid cancer – the development and spread of metastasis – and explain the strategy to overcome drug resistance secondary to intratumor heterogeneity. Unfortunately, none of the annotated targeted drugs have demonstrated clinical efficacy in inhibiting metastatic spread, or lack of resistance development.<sup>100</sup> Tannock<sup>101</sup> explains why intratumor heterogeneity may be a serious obstacle to precision treatments: “in the presence of heterogeneity, accurate genomic targeting is not possible, and resistant cells will be selected for survival”.

## PMs and drug resistance

Despite outstanding advances in medicinal chemistry, the development of resistance is the major limiting factor of precisely targeted treatments.<sup>102</sup> Vemurafenib (Zelboraf®), a B-Raf enzyme inhibitor, received marketing authorization in 2011 for the treatment of late-stage melanoma.<sup>103,104</sup> Near-miraculous initial results<sup>105</sup> were followed by the development of resistance and reappearance of the cancer within a year.<sup>106</sup> Unfortunately, and in contrast to received wisdom, cancer mechanisms have not gone from a black box to a blueprint yet.<sup>21</sup> The real chronicles of solid cancer R&D list unfulfilled promises and describe the triumph of hope and hyperbole over reality. This cycle of ecstasy and agony, as explained in the melanoma example, is mirrored in the experience of patients and their families, oncologists, and scientists.

In pharmaceuticals, imprecision has advantages, especially in multifactorial diseases. Multitargeted drugs and combinations have been successfully utilized for major chronic diseases such as hypertension, diabetes, and HIV/AIDS. Multikinase inhibitors in cancer generate much less resistance than selective ones.<sup>107</sup> When drug resistance develops to a targeted drug, initial combination therapy has merit.<sup>108,109</sup> In 2001, Goldie<sup>110</sup> suggested that the “magic

bullet” paradigm that had implicitly driven drug discovery until today needs to be changed to allow for the development of “magic volleys”. Fabbro,<sup>111</sup> in his review on 25 years of small molecular weight kinase inhibitors, states that the various mechanisms of drug resistance reflect the plasticity of cancer cells and the many ways by which a tumor can evade precision therapies. Terminology is important; for a successful strategic outcome, accuracy precedes precision, not the other way round. In 2016, precisely targeted monotherapy in solid cancer is futile, and pragmatic medicine (empiric combinations, imprecise medicine) may have advantages over PM, especially in the context of drug resistance.

In solid cancer, the established dogma for managing recurrent or refractory disease is that an increase in tumor size following shrinkage should prompt a change in therapy. However, favorable responses have been reported on drug rechallenge and treatment beyond progression.<sup>112,113</sup> These reports direct attention to the possibility of resensitization, or more analytically, a rethink of the operational definition of resistance. By “resistance” do we mean a new increase in tumor size, or a continuation of invasion and the metastatic process?<sup>47</sup> If it implies the former, then the benefit of continuing therapy beyond “progression” (an increase in size) is not unexpected. However, if it implies a new mutationally induced driver, then, by definition, a rechallenge should not work. Intra-tumor heterogeneity poses a serious obstacle to PM relative to treatment response and resistance, disease progression, and relapse. Within the context of tumor evolution, Jamal-Hanjani et al<sup>114</sup> have strategized translational approaches that involve combinatorial, adaptive, and tumor immune therapies.

Kang et al<sup>115</sup> have reported improvement in progression-free survival in gastrointestinal stromal tumour (GIST) patients following rechallenge with imatinib, suggesting that residual bulk disease may contain clones with continuing sensitivity. Nishida and Doi<sup>116</sup> extend this insight to targeted drugs in general and wonder whether radiographic disease progression (as assessed by RECIST criteria) always reflects disease progression and drug resistance?<sup>47</sup> Recently, Auliac et al<sup>117</sup> analyzed the impact of continuing first-line EGFR tyrosine kinase inhibitor (TKI) therapy beyond RECIST disease progression in patients with advanced EGFR-mutated non-small-cell lung cancer. There was no difference between the patients who did and did not continue TKI therapy with respect to progression-free survival (PFS1: 10.5 vs 9.5 months,  $P=0.4$ ). Overall survival (OS) showed a nonsignificant trend in favor of continuing TKI therapy (33.0 vs 21.2 months,  $P=0.054$ ). Accordingly, it is possible that with continuation of therapy, a delayed response, as

with oncoimmunologics, may be noted. If prospectively confirmed, and in the context of targeted drugs, a new increase in tumor size following a response may not signify progression of the disease, nor the development of “resistance”. Accordingly, it is possible that with continuation of therapy, a delayed response, as with oncoimmunologics, may be noted. However, the central question remains: if RECIST cannot predict failure, how can it predict success?

## Earlier detection of disease and its consequences

The aim of early detection is to identify disease at an earlier (asymptomatic) and curable stage. To be effective, antimetastatic drugs are required. Detection screens are not simple; there is a trade-off. Sensitive screens are not specific and may lead to false-positives (termed overdiagnosis), while specific screens can only detect advanced disease, which may not be curable. Early detection, especially if addressed with effective treatment that could delay the progression of disease, is the broader objective of screening.

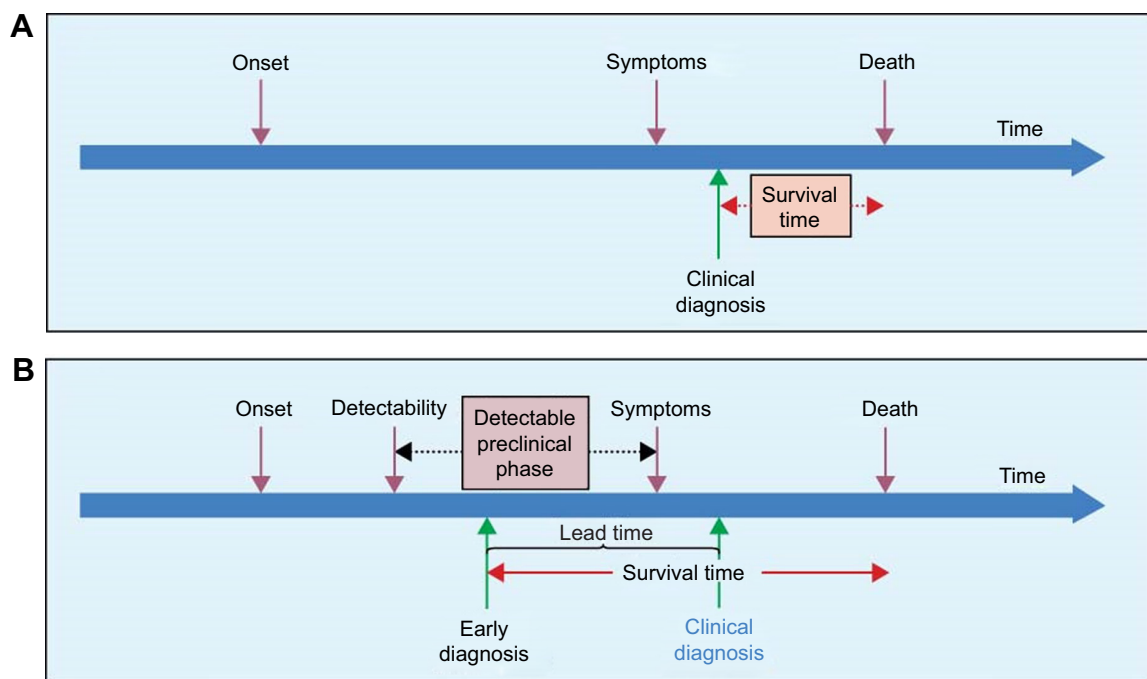
However, earlier detection inflates survival by:

- Lead time bias – the time of diagnosis is brought forward, to the left, ie, earlier<sup>118</sup> (Figure 7).
- Overdiagnosis – finding cancers never destined to progress at all, or which progress so slowly that the person dies of other causes.<sup>119–121</sup>

Clearly, intervention is not indicated for noncancers, but the consequences of false-positive results, namely, labeling, invasive testing to confirm a benign nature, and mental anguish, are serious considerations. This is demonstrated by the recent Korean Thyroid-Cancer “Epidemic”.<sup>122</sup> Thyroid cancer is now the most common type of cancer diagnosed in South Korea. More than 40,000 people in the country were diagnosed with the disease in 2011 – a figure that is more than 100 times the number of people who die from thyroid cancer, which for the past decade has been between 300 and 400 each year. Despite the surge in incidence, mortality was unchanged. False-positive individuals are now regarded as “cancer survivors”. This epidemic was a consequence of the addition of thyroid screening with ultrasonography to government-funded cancer screening tests. A year later, in 2015, and in response to increased awareness of overdiagnosis, a 35% decrease in thyroid surgery was noted.<sup>123</sup>

Esserman et al term these minor, noncancer abnormalities detected on screening as “indolent lesions of epithelial origin” (IDLE) and suggest that screening guidelines need to be revised to lower the detection of IDLE’s with the same energy used to increase sensitivity.<sup>119</sup> If not, and in contrast





**Figure 7** Lead time affects survival and incidence among patients who are diagnosed at screening, as the diagnosis is advanced in time and the disease is diagnosed earlier than under the circumstances of usual diagnosis without screening.

**Notes:** The figure shows the calculation of survival time for (A) a patient diagnosed clinically and (B) an asymptomatic individual diagnosed by screening. The early diagnosis in (B) has not postponed the time of death. Although survival time has increased, there is no benefit for the screen-detected patient. Reproduced from Bretthauer M, Kalager M. Principles, effectiveness and caveats in screening for cancer. *Br J Surg.* 2013;100(1):55–65.<sup>118</sup> With permission from John Wiley and Sons. Copyright © 2012.

to the expectations of Dzau et al,<sup>11</sup> genome diagnostics will likely increase the incidence of disease, and, exponentially, may qualify as the mother of all overdiagnoses and labeling. Here, Cho et al<sup>120</sup> make a relevant and important suggestion – cancer registries do not routinely collect the mode of diagnosis (ie, symptomatic or screened). The addition of this data, and partitioning of analyses, would further interpretation. The more sensitive the screen, the higher the incidence of IDLE. In their 2000 perspective, Holtzman and Marteau<sup>124</sup> explain that genotypes for common, complex diseases are incompletely penetrant, and correlations between the genotype and the phenotype are therefore weak. The operational consequences of incomplete genomic penetrance in common cancers are that there is a low magnitude of conferred risks, and therefore, a limited therapeutic potential for precision treatments.

It should be noted that the primary reason for screening is, with effective intervention, to extend meaningful life and delay mortality, not to reduce the incidence of disease. For primary prevention in populations, risk factor reduction makes more sense than genomic diagnoses, for example, smoking cessation and lung cancer. Genomic diagnostics may identify possible markers of early disease, but appropriate intervention is required to slow progression. To advocate

a rush to develop genomic diagnostics before revising regulations governing useful drug approval, and refining screening guidelines and reporting, is to put the cart before the horse. In solid cancer, without effective medicines, an extension of useful life, via screening only, is an illusion.

A valuable insight into the perils of indiscriminate cancer screening has recently been publicized by Gilbert Welch and Peter Albertsen<sup>125</sup> at The Dartmouth Institute and University of Connecticut Health Center, respectively: the heterogeneity in cancer can be described through the metaphor of birds, rabbits, and turtles. The goal of early detection is not to let any of the animals escape the barnyard and cause a cancer death.

- But the birds have already flown away. They are the most aggressive cancers, the ones that have already spread by the time they are detectable, the ones that are beyond cure.
- The rabbits, potentially lethal cancers that might benefit from treatment, are ready to hop out at any time. These are the cancers we hope to control with early detection.
- Then there are the turtles – these are nonlethal cancers that are not going anywhere. Screening is really good at finding these cancers.<sup>125</sup>

Following Hall et al,<sup>30</sup> before genetic screening is launched on a national scale, the following criteria need to be satisfied.

- Genomic information will predict disease risk better than phenotypic information.
- Cost-effective interventions exist for those at increased genetic risk.
- These interventions will be more cost effective than population-level interventions.
- Genetic risk information will motivate desired behavior change.

Currently, and for the foreseeable future, there are no examples of genetic screening for disease risk that satisfy these criteria.<sup>30</sup>

## Genes and the environment

Gene–environment interactions are fundamental to the pathogenesis of disease, especially cancer; these influences cannot be separated. In some cancers, genetic determinants predominate, while in others, the environment is more relevant. Genetic factors usually dominate individual susceptibility but do not explain population differences in incidence. And genetic heterogeneity is much greater within, than between, populations. This is opposite to that seen for environmental factors. Several types of cancer vary in incidence by more than an order of magnitude between different populations. The convergence toward local cancer rates seen among immigrants excludes a genetic explanation of these differences.<sup>18</sup> A high-penetrance gene defines the phenotype in individuals who carry it. A weakness of the PM logic in oncology is a consequence of the incomplete penetrance of genotypes in solid cancer, the limited ability to tailor treatment to genotypes, and the low magnitude of risks conferred by various genotypes for the population at large. The vast majority of solid cancers are associated with low penetrance genes that require an environmental contribution to allow for expression. It would be truly revolutionary if we could determine the genotypes of the majority of people who will get common cancers.<sup>124</sup>

In 1985, Geoffrey Rose<sup>18</sup> demonstrated that the determinants of the population distribution of disease have less to do with the individual-level risk factors that promote disease within a population, and more to do with the macrolevel structural causes that shape entire distributions of disease across populations. As a young scientist, his grant application was rejected because the reviewers stated that even in national/international programs, clinical research should concentrate on individuals, not populations. The opposite

opinion is now a fundamental principle in epidemiology and environmental medicine: the population carries a collective responsibility for its own health and well-being, including that of its deviants (those with disease).<sup>126</sup>

In 2015, Keyes et al<sup>127</sup> at the Columbia University, New York, USA, analyzed the mathematical limits of genetic prediction for complex chronic disease, and confirmed Rose's 1985 insight. When common germline genetic variants are insufficient to produce disease, the predictive capacity of the genetic variant alone will be determined by the prevalence of factors that interact with the variant and the rate of the disease in the population. Genetic variants will be strong predictors of disease only when the factors that interact with the disease are common and when the background rate of disease is rare.

## 21st Century Cures Act

In May 2015, the 21st Century Cures Act was introduced in the US House of Representatives, with the goal of promoting the development and speeding the approval of new drugs and devices.<sup>4,11</sup> In committee, the Bill was approved unanimously (51-0). The main focus was funding for the National Institutes of Health/NCI, and reform at FDA toward simplifying and accelerating the new drug and diagnostics approval process, and incorporating PM-related elements,<sup>3</sup> specifically the inclusion of genomic-based biomarkers and surrogate end points in clinical trials. Several “simplifying proposals”, namely, a reliance on clinical experience, observational studies, and registries, instead of randomized, controlled trials, and on biomarkers and other surrogate measures rather than actual clinical end points, are used to define clinical outcome. Gonsalves et al,<sup>128</sup> leaders in regulatory science, have stated that these proposals could lead to the weakening of FDA's process and controls, and to the approval of drugs that are less safe or effective, or trial failure of a truly innovative medicines. In their opinion, it is unlikely that better drugs would emerge via diluted regulations.

## Program costs

Today, cancer drug pricing is dominating the news. At the 2015 American Society of Clinical Oncology meeting, Dr Leonard Salz of the Memorial Sloan Kettering Cancer Center, New York, stated: These drugs cost too much. PM emphasizes expected benefits to patients but is silent on costs. Recently, 100 oncologists presented an initiative to lower cancer drug prices,<sup>129</sup> but the proposal did not define the effectiveness and value of drugs for solid cancer – is metastasis delayed and is there an extension of meaningful

life?<sup>22</sup> Efforts to lower the price of ineffective drugs may be to miss the point? Young<sup>130</sup> notes that the costs of cancer drugs amount to only 5%–20% of the total costs of cancer care, depending on how many of the multiple cost components are included. Accordingly, and to be fair, attention may also be directed to the costs of care that are determined and driven by oncologists, hospitals, and health insurance.

Advances in sequencing have accelerated the identification of several new gene mutations or amplifications that may be appropriate for genomic-driven diagnostics and drug development. We assume that with the significant decline in the costs of goods – genomic sequencing – R&D costs will undergo a similar decline, and that pricing for PM-translated drugs will be affordable<sup>7</sup> (Figure 8).

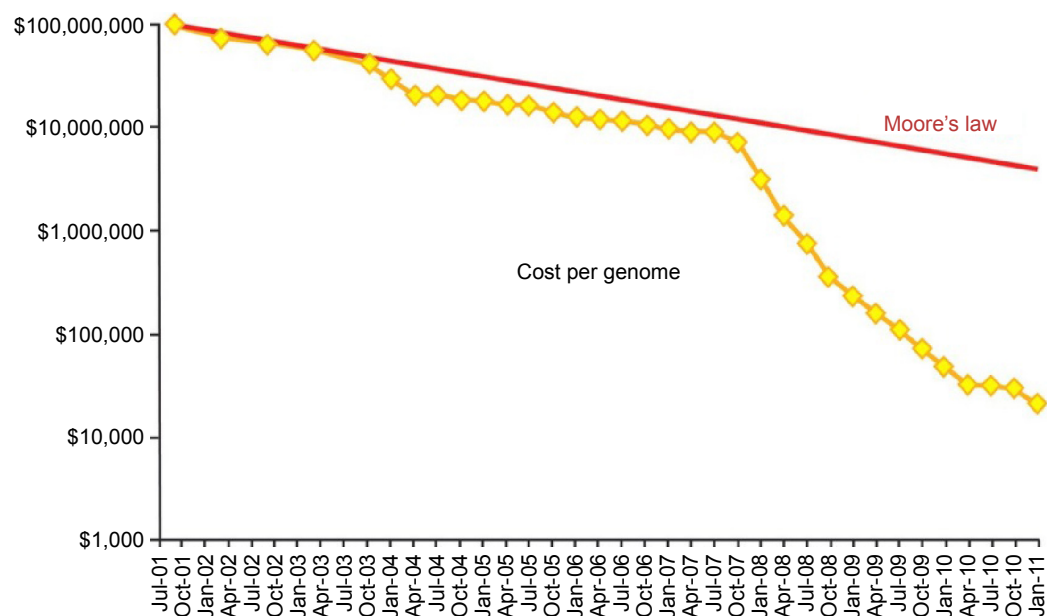
The dramatic drop in costs of sequencing technologies in genomic testing has resulted in widespread consumer marketing. These tests provide individual risks for several complex diseases and phenotypic traits, and are targeted to healthy individuals as a form of genomic screening. Bunnik et al<sup>131</sup> suggest that a rethink of medical evaluation and regulation, with a focus on the reduction of harm, may be necessary and timely.

In contrast to most research-intensive industries, consumer electronics for example, we have not seen improved medicines at affordable prices. Disruptive invention occurs in academic and pharma laboratories, but regulations both

favor and force the development of commodity drugs – tumor shrinkage. As a consequence, pricing is unrelated to novel utility and meaningful benefit to patients, but based solely on what the market can bear.<sup>24</sup> Clearly, the business model is broken, and can only be corrected by a regulatory and reimbursement rethink from a rational and public health standpoint. With strong and disciplined stakeholder efforts, we have succeeded with HIV/AIDS in both high- and low-income countries.<sup>26,27,132</sup> Why not in solid cancer?

## The cancer “moonshot” program – 2016

Overall, the PM initiative should be viewed as an encouragement to the furtherance of science in the service of medicine. It would be best for scientists and physicians to outline the program. Unfortunately, in this case, the government has identified genomics as the sole platform for diagnostics and therapeutics. Complex diseases require multidisciplinary effort, and the PM initiative with its emphasis on genomics may exclude related disciplines of epidemiology, pharmacology, biology, chemistry, and especially public health, from recognition and support. In 2015, universities have already created Genome Institutes, and we note a migration of students toward these institutes and away from traditional and proven disciplines. When asked for the reason, they quote the legendary bank robber



**Figure 8** Will a lower cost of goods lead to lower prices for PMs?

**Notes:** The cost of whole-genome sequencing is plotted as a function of time. Notably, since 2007 genome sequencing costs have declined faster than that predicted by Moore's law. Reproduced from Salari K, Watkins H, Ashley EA, Personalized medicine: hope or hype? *Eur Heart J*, 2012;33(13):1564–1570<sup>7</sup>, by permission of Oxford University.

**Abbreviation:** PM, precision medicine.

Willie Sutton, who replied to the judge's inquiry as to why he robbed banks by saying "because that is where the money is". If prudence and caution are not exercised, Vice President Biden's "moonshot" program, based on the promise of genomics, may suffer the same fate as a previous plan based on retrovirology.<sup>133</sup>

## Conclusion – Paul Ehrlich: *magister mundialis pragmatice medicine*

The fundamental question is: whether conventional research in solid cancer therapeutics is on the right track, and if not, is PM the solution?<sup>1</sup> The answer requires serious introspection.<sup>134</sup> All things considered, we arrive at the impression that the PM initiative represents a technology push driven by the rapidly decreasing costs of genomic technology (solutions), rather than a demand pull (patient needs). Consistent with PM strategy, Dyson,<sup>135</sup> at the Institute for Advanced Study, Princeton, in clear contrast to Kuhn,<sup>20</sup> makes a case for the primacy of new tools, rather than new ideas as a driver of innovation. However, the enthusiasm toward genomic technology, especially screening,<sup>11</sup> in the absence of a novel disease/treatment paradigm, may be akin to the tail wagging the dog. In solid cancer, advances in technology may have outpaced an understanding of disease, and medical and public health issues may not have been addressed in a thoughtful, structured, and disciplined manner.<sup>15,30,31,64,124,136</sup>

PM is predicated on a complete understanding of disease mechanisms. According to the Centers of Disease Control and Prevention (USA), sickle-cell disease is a life-threatening disorder that affects millions of people throughout the world and is particularly common among those whose ancestors came from sub-Saharan Africa; Spanish-speaking regions in the Western hemisphere (South America, the Caribbean, and Central America); Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy. The disease affects nearly 100,000 individuals of African origin in the USA.<sup>137</sup> A complete understanding of the mechanism of sickle-cell anemia has been known for over a half century, but we are still awaiting a PM. While we are still far from a precise understanding of mechanisms of hypertension, diabetes, and infectious diseases, especially HIV/AIDS, this has not prevented the development of medicines that are meaningfully effective, globally available, and affordable. Bentires-Alj et al<sup>138</sup> explain that translational research leaves no one indifferent, and everyone expects a particular benefit. The collective objective is to identify measures to promote translational research without undermining basic

exploratory research and academic freedom. Multidisciplinary basic research should be translated in a pragmatic manner.<sup>68,138</sup>

The American philosopher, James (1842–1910),<sup>139</sup> explains that pragmatism is a new name for some old ways of thinking, namely, the test of expected utility. He states that pragmatism emphasizes practical consequences in determining the criterion of meaning, truth, or value. The relationship of pragmatism to translation is obvious and focuses on the development of products that demonstrate meaningful efficacy, here, and now. He advises that applicable knowledge is derived from verified facts and actions, rather than "logical proofs, or principles, or databases". We consider Paul Ehrlich (1854–1915), as the father of pragmatic medicine.<sup>140,141</sup> When the world, a century ago, faced an epidemic scourge, syphilis, Paul Ehrlich and Sahachiro Hata, with training in biology and chemistry, but scant resources, initiated an R&D program on organic arsenicals. In 1910, after 605 failures, they synthesized and marketed the first, relatively safe, and effective treatment for syphilis – Salvarsan or compound 606.

In 2010, Ledford<sup>142</sup> reported that the cancer database would soon be flooded with genome sequences from 25,000 cancers, and interpretation would be the challenge. If asked, William James would tell us that building a bigger haystack is not the best way of finding the needle. And he would likely agree with Roberts et al<sup>143</sup> at the Johns Hopkins, Baltimore, MD, USA, who states that it is going to take good old-fashioned biology to really determine what is going on. But today, the prospects of getting funded for good old-fashioned biology are slim, if any. Again, it is self-evident that without multidisciplinary basic research in biology, there will be little to translate.<sup>68</sup>

The promise of huge clinical and monetary benefits of the PM initiative, as outlined by Collins and Varmus<sup>3</sup> and Dzau et al,<sup>11</sup> is based on the expected prediction of common multifactorial diseases using an economic simulation model. Roberts et al<sup>143</sup> had earlier demonstrated that an analysis on whole-genome sequencing of monozygotic twin pairs (twins of a pair share the same genome type and therefore identical genetic risk factors) did not predict risk of most of 24 common diseases, including type 2 diabetes, cancers, stroke, and coronary heart diseases.<sup>144</sup> On the one hand, Matuchansky,<sup>144</sup> at the Diderot University, Paris, questions the prediction made by Dzau et al<sup>11</sup> that PM would lead to substantial cumulative gains (expressed using US\$100,000 per quality-adjusted life-year, with a \$33 billion gain at a reduced disease incidence of 10% and up to a \$607 billion gain at a 50% incidence reduction) in life expectancy and



quality-adjusted life expectancy during the subsequent 50 years. He states that the proposed alignment of incentives to fulfill the potential of PM is only a promise drawn from a model, which is, itself, still a promise.<sup>144</sup> On the other hand, Doble et al<sup>145</sup> at the Garvan Institute, Australia, agree that genomics may have a role in population health. However, and in contrast to Dzau et al,<sup>11</sup> the priority and benefits of PM will be limited to individuals at high risk of imminent, serious, preventable, penetrant disorders that have large health-care costs. These expert views have important implications for the valuation of new genomic initiatives by industry, public policy makers, university administrators, health insurance companies, patients, and of course, cancer-funding agencies. Following Welch,<sup>123,125</sup> we hope that examples cited here will encourage physicians to find their voice when medical trends run counter to their patients' interests.

The challenge facing precision oncology is huge; solid cancer is not a single entity, and as noted may involve 25,000 cancer subtypes. Complexity aside, the cost of R&D for precision diagnostics and drugs, especially clinical trials, and regulatory requirements, would be enormous. Here, pragmatic medicine offers guidance and advises that we focus on "common denominators and not differences". Cancer is conventionally classified as hematologic or solid. In hematologic cancer (eg, leukemias), clonal proliferation is the predominant mechanism,<sup>93</sup> while solid cancer is mainly characterized by tissue invasion and metastasis, and the cancer tumor microenvironment (stroma) displays varying degrees of desmoplasia.<sup>47,146</sup>

Tissue invasion and metastasis relies primarily on motility and migration of the cancer cell,<sup>77,80–84,94,147</sup> assisted by epithelial–mesenchymal plasticity,<sup>83,86,148–151</sup> while desmoplasia is a consequence of fibroblastic activity. Economy of effort suggest that attention be best directed to inhibiting cell motility and factors promoting cell aggressiveness, namely hypoxia<sup>83,151</sup> and desmoplastic containment of the cancer stroma.<sup>146,152</sup> Whatcott et al<sup>152</sup> assessed desmoplasia in metastatic lesions of pancreatic ductal adenocarcinoma and compared it with that of primary tumors. Both primary tumors and metastases had a highly fibrotic stroma. A negative correlation was noted between patient survival and extracellular matrix (collagen I or hyaluronan) deposition. The authors suggest that stromal-targeting agents have the potential to benefit patients with solid cancer, even those with metastatic disease.<sup>152</sup> We infer that a focus on the initial steps in the metastatic cascade may be more rewarding than exploring downstream mechanisms complicated by dense signaling cross-talk.

In this context, we draw attention to lines of inquiry that illustrate the pragmatic approach in solid cancer: that of Cox and Erler<sup>153</sup> at the Biotech Research and Innovation Centre, Copenhagen, on their work on connecting tissue stiffness, fibrosis, and solid tumor metastasis; and Olson et al at the Cancer Research UK Beatson Institute, Glasgow; the late Marshall et al at the Institute of Cancer Research, London; and Yun et al at the Penn State Hershey College of Medicine, USA, on the demonstration of Rho kinase/MRCK inhibitors in blocking cancer cell migration and metastasis.<sup>154–156</sup>

In conclusion, we hope that a consideration of the points raised in this essay may be relevant to the ongoing debate on PM and the 21st Century Cures Act. In particular, the successful HIV/AIDS program serves as a global model of Pragmatic Medicine in operation – tangible utility, here, and now. We should recall with both pride and humility that this program was a pragmatic, community-initiated, translation-driven, regulatory-supported, public health initiative, and a direct response to expressed need of patients and their families. It can be repeated for solid cancer!

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## Author contributions

All authors contributed equally, made substantial contributions to the conception, design, and drafting this essay, and have approved the final version.

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