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Perspectives on personalized cancer care

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Summary

Sir William Osler has been quoted as saying “*If it were not for the great variability among individuals, medicine might as well be a science and not an art*”. Molecular profiles, be they host or those providing insight into the genomic changes that define a cancerous cell, together possess the predictive ability required for the various aspects of individualized care: risk assessment, patient prognosis, and prediction of therapeutic responses. Such profiles, obtained by RNA, DNA and protein microarrays, SNP arrays, methylation screens, and high throughput or targeted gene sequencing can provide patient- and tumor-specific information that details the biological complexity of a particular cancer and can be exploited to understand its clinical implications and glean therapeutic insights. This knowledge is also being combined with host factors to begin formulating an understanding at the system level of how the tumor interacts with the host and how this relationship can be exploited therapeutically or for biomarker development. Here we discuss these advances and how they may relate to urologic oncology.

Perspective

Cancer is a genetic disease [1]. A cancer cell inherits or acquires mutations that enable it to grow efficiently, replicate indefinitely, support angiogenesis, avoid apoptosis, and in some cases metastasize [2]. Fortunately, molecular profiles obtained by RNA, DNA and protein microarrays, SNP arrays, methylation screens, and high throughput or targeted gene sequencing have begun to reveal (directly or indirectly) which mutations drive the cancerous phenotype compared to being passengers on this malignant journey. Notwithstanding the role of individual genes, the aggregate molecular profiles provide patient- and tumor-specific information that details the biological complexity of a particular cancer and can be exploited to understand its clinical implications and glean therapeutic insights. This knowledge is also being combined with host factors to begin formulating an understanding at the system level of how the tumor interacts with the host and how this relationship can be exploited therapeutically or for biomarker development. Importantly, interactions involving both the local tissue microenvironment and distant organs [3], and psychological factors such as stress [4] influence tumor growth and disease progression. Prior to cancer development, molecular analysis of the host can ascertain the risk of cancer development especially as it relates to a variety of exposures such as smoking.

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Because each patient and each tumor is unique, an optimal clinical strategy for one individual may be sub-optimal or fail completely in another. Rather than using a *population*-based, “one size fits all approach” to cancer prevention and management, individualized care involves using molecular profiles to guide clinical care decisions independently for each *individual*. The goal of individualized care is to provide optimal prevention, follow-up and treatment strategies while minimizing toxicities, unnecessary risks, and superfluous medical costs.

An individualized approach to cancer care seeks answers to the following patient-centric questions. 1) Is this patient at risk of developing cancer, prior to any clinical manifestations of disease (risk assessment) and what exposures are the most relevant? 2) In this patient, is treatment necessary following neoplasm discovery (patient prognosis)? 3) If treatment is warranted in this patient, which treatment and what dosage will be most effective (predicting therapeutic response)? Here, we comment on risk assessment, patient prognosis, and predicting therapeutic responses. Finally, we conclude with some thoughts about the future of individualized cancer care in the 21st century.

Risk assessment: is this patient at risk?

The path towards individualized risk assessment began with the use of family histories to identify at-risk patients [5]. However, because not all individuals with family histories inherit the mutations that carry hereditary risk [6], patients with family histories have historically been subjected to testing. Whereas the use of family histories alone can only measure *family* risk, genetic screening measures *individual* risk and allows clinicians and patients to make better informed decisions regarding the intensity of surveillance, the need for pre-emptive surgery, and behavioral risk avoidance. The National Human Genome Research Institute, for example, recommends early breast and ovarian cancer screening for individuals carrying *BRCA1* or *BRCA2* mutations, but not early screening otherwise [7].

The number of known cancer mutations associated with disease susceptibility has grown exponentially in the last fifteen years [8]. The GeneTests web site, hosted by the National Center for Biotechnology Information (NCBI), provides “current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counseling” and presents expert authored disease descriptions for nineteen cancers, including breast, ovarian, colon, esophageal, lung, and prostate cancer [9]. Ongoing large-scale efforts to publicly catalogue cancer mutations, such as the literature-derived Catalogue of Somatic Mutations in Cancer (COSMIC) [10] and the *ex vivo*-derived Cancer Genome Atlas, based on molecular profiles of human tissues [11], will lead to an increase in the number of genetic tests available. Several publicly available personalized medicine resources are provided in Table 1.

Recently, concerns about the number of available genetic tests (over 900) and direct to consumer marketing have prompted the American Society of Clinical Oncology (ASCO) to issue an updated policy statement emphasizing the need for clinical utility and genetic counseling in conjunction with test administration [12]. For both patients testing positive or negative from the currently available tests, the correct interpretation of these becomes

paramount given the potentially dramatic psychological and behavioral impact these may have. Indeed, the social, ethical, and privacy concerns inherent in genetic testing are not trivial and must be addressed [13]. However, although privacy concerns remain, it is reassuring that the passage in the United States of the Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits insurance companies and employers from discriminating against an individual based on that person's genetic profile [14].

Prognosis and early detection: should this patient be treated?

Screening and early detection have clearly been instrumental in decreasing cancer mortality rates in some tumor types [15]. Early detection has conventionally relied on physical exams, imaging techniques, and histological or cytological screening. However, the identification of proteomic [16], micro-RNA [17], and epigenetic [18] biomarkers that detect cancer in its nascent stages suggests that biomarker screening will become more routine over time. Conceivably, a multiparameter evaluation of several body fluids in the future may provide a "health check" that could be used to obviate or reduce routine physician visits.

Although cells can undergo transformation, not all transformed cells progress into clinically detectable cancers and of those that do, not all of them harm the patient either by reducing quality or quantity of life. As urologists, prostate cancer is without a doubt one of the cancers that exemplifies this phenomenon most closely for us. However, it is observed in several other cancer types. For example cervical dysplasia progresses to invasive cancer in less than 50% of patients without treatment [19]. Should all of those patients receive treatment? Understandably, precaution generally guides clinical decisions, i.e. it is better to receive treatment based on the assumption that cancer will develop (even though it may not), than to forsake therapies and risk cancer progression. This approach explains why, for example, the majority of individuals with ductal carcinoma in situ (DCIS) are treated for invasive breast cancer, even though their cancer progression rate is generally below 50% [20]. Furthermore, only around 11% of patients diagnosed with DCIS who undergo lumpectomy alone develop invasive breast cancer within 8 years, yet more than 60% of diagnosed individuals choose complete mastectomy or lumpectomy in conjunction with radiation treatments or hormone therapies [21]. The role of molecular profiles is to stratify patients into low and high risk groups in order to better inform clinical decisions. Appropriate treatments are recommended for those likely to progress while treatment is not recommended for those less likely. In patients with DCIS, protein biomarkers have been used to weed out a low risk group with only a 4% chance of developing invasive breast cancer within 8 years [21].

While the above examples were of early in situ malignancies, the role of personalized tools has been successfully applied to assessing the risk of patients with established and treated cancers. The urological literature contains several examples of validated prognostic nomograms using conventional anatomic and pathological markers that offer clinical utility [22, 23]. While these tools are useful for both providing a risk profile to the patient as well as constructing an effective follow up strategy, there is an increased emphasis on the development of molecular markers to form new prognostic tools either alone or in combination with classical markers with the hope of providing superior predictive

performance. In addition, molecular profiles may, by virtue of looking at distinct cellular pathways in the tumor more precisely, provide assistance with clinical decisions regarding adjuvant therapies to prevent recurrence and metastasis. Perhaps the most well-known validated and widely used tool for assessing tumor recurrence is the *Oncotype DX*TM test for breast cancer, which provides a recurrence score based on an expression profile of 21 genes. The recurrence score accurately correlates with 10-year recurrence rates and helps patients decide whether chemotherapy is appropriate [24]. Among others, gene expression profiles that predict recurrence in non-small lung cancer [25] and breast cancer metastasis in five years [26] have also been described and retrospectively validated. For all these tests, whether based on classical or molecular variables, their validation on distinct datasets, preferably from prospectively collected samples from patients involved in clinical trials, is paramount. Without such stringent evaluation, their utility may be in question.

Predicting therapeutic responses: what treatment is best for *this* patient?

Once it has been decided that a patient needs systemic treatment either for a primary tumor in the neoadjuvant setting; following treatment in the adjuvant setting; or for a metastatic recurrence, the key decision is what regimen to choose. The optimal treatment choice should have a high probability of success and a low probability of toxicity and other unwanted side effects. However, historically the optimal choice of treatment has in most cases been developed from studies in biologically unselected populations. The use of molecular profiles to guide treatment decisions based on predicted therapeutic responses is an integral part of individualized care. In addition, the selection of probable responders in clinical trials will increase the statistical power for demonstrating drug efficacy and therefore increase the number of treatment options available. There are striking examples where a molecular understanding of cancer biology has led to dramatic therapeutic advances. In addition, pharmacogenomics has provided some key insights into drug metabolism and processing and has allowed the optimization of therapies. Together looking at the host and the tumor will provide the most useful picture to guide cancer therapy.

Predictions of therapeutic responses

The prediction of treatment outcomes based on molecular profiles assesses the appropriateness of a proposed treatment. Gene expression profiles have been used to predict 10-year distant recurrence rates in breast cancer patients following cyclophosphamide, methotrexate, and fluorouracil or methotrexate and fluorouracil chemotherapy with five years of tamoxifen treatment [27]; and response to platinum-based chemotherapy in patients with advanced stage ovarian cancer [28]; and mutations in epidermal growth factor receptor (EGFR) can predict response to gefitinib treatment in patients with recurrent lung cancer [29]. In general, micro-RNA polymorphisms influence drug sensitivity and resistance [30]. In bladder cancer there are several studies that have made progress towards this end. In the neoadjuvant setting, Takata *et al.* recently employed a cDNA microarray platform to profile gene expression from biopsies of 27 invasive bladder cancer patients who were subsequently treated with MVAC neoadjuvant chemotherapy [31]. Another study examined cisplatin based combination chemotherapy (MVAC and GC) in 30 patients with locally advanced or metastatic invasive bladder cancer (T4b, N2-3 or metastatic M1). Als *et al.*, used an

oligonucleotide microarray platform to profile the gene expression of tumors from these patients and related it to survival [32]. A set of 55 genes were discovered to be differentially expressed between these groups; interestingly, all 55 were underexpressed in patients with long term survival.

Predicting therapeutic responses from *in vitro* testing

The use of molecular profiles to predict treatment outcomes requires one clinical trial to identify the profile and a second independent clinical trial to validate it. This strategy, although promising, has the disadvantage of being time-consuming and expensive. The strategy is not amenable to predicting treatments for rare orphan tumors and is limited in therapeutic scope. In addition, it is not amenable to the rapid development of biomarkers to regimens that include new drugs before clinical trials are carried out. A radical and innovative strategy was recently proposed that extrapolates *in vitro* drug response data to make *in vivo* predictions based on the gene expression profiles that are common to both. This approach called COXEN (COeXpression Extrapolation) uses expression microarray data as a “Rosetta Stone” for translating between drug activities in a cancer cell line panel to drug activities in a set of clinical tumors. Using the National Cancer Institute (NCI) collection of 60 cancer cell lines (NCI-60) [33], their gene expression profiles [34], and drug sensitivity data on over 100,000 compounds, Lee *et al.*, used COXEN to predict sensitivity to cisplatin and paclitaxel chemotherapies in bladder cancer cell lines and sensitivity to docetaxel and tamoxifen in breast cancer patients, and also demonstrate the utility of COXEN in drug screening [35]. This approach was used to identify a promising new agent in bladder cancer called C1311 [36] while successfully predicting the response of bladder cancer patients to chemotherapy both in the neoadjuvant and treatment settings [37].

Targeted therapies

Analyzing molecular profiles for genetic disruptions and signaling pathways involved in a specific cancer can identify therapeutic targets and appropriate populations for treatment. The development of a kinase inhibitor following the discovery of a dysregulated ABL tyrosine kinase in chronic myelogenous leukemia is one example [38]. Another example is the targeted use of trastuzumab, a monoclonal antibody specific for the HER-2 receptor. In breast cancer patients, the response rate of trastuzumab at the population level is approximately 10%, but grows to 35–50% when individuals are selected on the basis of HER-2 overproduction [39]. In general, the observation that gene expression profiles that predict pathway deregulation also predict drug sensitivity to therapeutic agents that target those pathways suggests a framework for developing targeted therapies [40].

Pharmacogenomics

Optimal drug dosage depends on how genetic variability influences the metabolism, absorption, transport, and processing of therapeutic agents. The oral anticoagulant warfarin is a classic example of a drug with pharmacogenomic influences, where single nucleotide polymorphisms in the genes *CYP2C9* and *VKORC1* have been shown retrospectively to influence warfarin metabolism and sensitivity [41]. In cancer, the toxicity of mercaptopurine, an agent used to treat acute lymphoblastic leukemia, depends on

polymorphisms in thiopurine methyltransferase (TPMT). Genetic tests can identify patients likely to experience fatal toxicities if given conventional dosages [42].

Conclusions and Perspectives

Sir William Osler has been quoted as saying “*If it were not for the great variability among individuals, medicine might as well be a science and not an art*”. Molecular profiles, be they host or those providing insight into the genomic changes that define a cancerous cell, together possess the predictive ability required for the various aspects of individualized care: risk assessment, patient prognosis, and prediction of therapeutic responses. Although individualized care will limit the amount of unnecessary testing and treatment, there are always benefits and risks associated with any clinical decision. A clear explanation of benefits and risks is necessary for effective shared decision making between physician and patient to occur [43]. Importantly, the quantitative nature of individualized care needs to be presented in a framework that a patient can understand [44]. Hopefully, as more data is collected about the cancer genome, and the complex relationships between molecular profiles and cancer phenotypes is illuminated, clearly optimal strategies for individual patients will emerge.

As research into individualized care continues, we expect to see advances in the following areas: 1) multi-step approaches that, e.g., propose a targeted therapy for individuals where drug resistance to a standard drug is likely [28]; 2) integrated approaches that utilize distinct and complementary molecular profiles, e.g., gene expression data and genomic data and proteomic evaluation; 3) multivariate approaches that achieve high statistical accuracy by utilizing molecular profiles with traditional risk factors such as age and gender; and 4) adaptation of current approaches to new biotechnologies that become available.

For personalized medicine to reach its full potential, however, pharmaceutical business models, economic incentives for health insurers and providers, and regulatory requirements must align with individualized clinical care objectives. Pharmaceutical companies that traditionally invest in drugs whose payouts come from wide use despite relatively low population-wide success rates must now consider changing the business model and invest in drugs that are applicable to smaller numbers of patients but whose increased effectiveness will ensure wider use in that smaller population. While biomarker discovery should also become part of the drug development pipeline, uncertainty regarding the cost and reimbursement of for diagnostic tests in the United States has hindered progress in this area. Uncertainty regarding regulatory requirements also slow progress in this area. For example, are retrospective studies on prospectively collected samples acceptable for approval of diagnostic tests, and can Phase III clinical trials be limited to the biomarker positive individuals who are most likely to benefit from treatment? Nevertheless, a paradigm shift towards personalized medicine is clearly underway. According to a recent survey, biomarker programs accompany 30–50% of drugs that are currently in development [45]. This shift will undoubtedly continue as commercial and academic involvement is further supported by federal resources and infrastructure, including a forthcoming Genetic Testing Registry (hosted by NIH) that will provide data on FDA approval and clinical utility of diagnostic tests [46].

In conclusion, the biological complexity of cancer and pharmacogenomic variability among individuals that influences treatment responses should not be underestimated. Nevertheless, recent advances in individualized care and in the economical utility of the biotechnologies that support it are promising and are rapidly leading to transform the face of medicine as we know it.

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Table 1

Examples of publicly available personalized medicine resources

Resource	Description	Ref
Personalized Medicine Coalition	Educational resource with news and policy initiatives	[1]
GeneTests (NCBI)	Information on genetic testing	[2]
Catalogue of Somatic Mutations in Cancer (COSMIC)	Literature-derived database of cancer mutations	[3]
Cancer Genome Atlas	Cancer mutation database obtained from molecular profiling	[5]
International HapMap Project (NCBI)	Database of common genetic variants	[6]