Precision Medicine for Cancer

Subjects: Oncology

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The diagnosis and treatment of diseases such as cancer is becoming more accurate and specialized with the advent of precision medicine techniques, research and treatments. Reaching down to the cellular and even sub-cellular level, diagnostic tests can pinpoint specific, individual information from each patient, and guide providers to a more accurate plan of treatment. With this advanced knowledge, researchers and providers can better gauge the effectiveness of drugs, radiation, and other therapies, which is bound to lead to a more accurate, if not more positive, prognosis. As precision medicine becomes more established, new techniques, equipment, materials and testing methods will be required. Herein, we will examine the recent innovations in assays, devices and software, along with next generation sequencing in genomics diagnostics which are in use or are being developed for personalized medicine. So as to avoid duplication and produce the fullest possible benefit, all involved must be strongly encouraged to collaborate, across national borders, public and private sectors, science, medicine and academia alike. In this paper we will offer recommendations for tools, research and development, along with ideas for implementation. We plan to begin with discussion of the lessons learned to date, and the current research on pharmacogenomics. Given the steady stream of advances in imaging mass spectrometry and nanoLC-MS/MS, and use of genomic, proteomic and metabolomics biomarkers to distinguish healthy tissue from diseased cells, there is great potential to utilize pharmacogenomics to tailor a drug or drugs to a particular cohort of patients. Such efforts very well may bring increased hope for small groups of non-responders and those who have demonstrated adverse reactions to current treatments.

Keywords: precision medicine ; genomic ; proteomic ; metabolomics ; biomarkers ; pharmaco-genomics ; cancer

1. Introduction

The diagnosis and treatment of diseases such as cancer is becoming more accurate and specialized with the advent of precision medicine techniques, research and treatments. Reaching down to the cellular and even sub-cellular level, diagnostic tests can pinpoint specific, individual information from each patient, and guide providers to a more accurate plan of treatment. With this advanced knowledge, researchers and providers can better gauge the effectiveness of drugs, radiation, and other therapies, which is bound to lead to a more accurate, if not more positive, prognosis. As precision medicine becomes more established, new techniques, equipment, materials and testing methods will be required.

2.Benefits of Personalized Medicine

With each new discovery, pharmaceutical success, and patient recovery gained through precision research, development and implementation, personalized or precision medicine is becoming recognized as a powerful approach in preventing and fighting cancer and many other diseases. Detailed molecular profiles of individuals' organs, cells, and tumors are proving much more powerful than pathology alone in guiding our response. The ability to track the progression or regression of a tumor over time, using the ever-expanding array of biomarkers available, is combining with pharmacological advances to focus treatments for a specific population, ethnic group, or tumor type. As an example of potential for precision medicine to benefit one population subset, earlier, improved assessment and treatment would clearly benefit pediatric cancer patients[1].

In this review, we shall discuss present knowledge, strategies and treatments for precision oncology, as well as their clinical applications. Within the larger field, pediatric oncology represents an area of both challenge and triumph for cancer research and treatment. One major difficulty in this field centers on the fact that the genetic makeup of pediatric tumors provides fewer targets than with adult tumors. Despite this, the survival of pediatric leukemia and tumor patients has greatly improved in recent decades, due to new combinations of treatment modalities, focus on cytotoxic chemotherapy to aid those most at risk, and the discovery and refinement of novel biologic markers, all of which are combined with more traditional clinical and histologic strategies and treatments. In addition to these, genomic research is opening up new points of attack: mechanistic insights, "driver" genomic alterations, aberrant activation of signaling pathways, and

epigenetic modifiers, any of which may provide new targets for precision pharmaceuticals or other treatments. Taken together with previous knowledge and approaches, this epigenetic and genomic data greatly increases our ability to understand childhood cancer and to produce more positive outcomes both for toxicity and survival rates. Given more time, investment and discovery, advances in precision oncology will undoubtedly continue to produce more and better practical applications and results for children and adults alike.

As another example of the power of precision medicine, biomarkers, along with human epidermal growth factor receptor 2 (HER2) have become an important tool for breast cancer detection and treatment. This beneficial development has opened the door to a host of important advances. As these breakthroughs continue, and our knowledge is strengthened and refined, the combined fields of medicine, pharmacology and health care will advance. With further enhancements and refinements, we will develop pharmaceuticals, equipment and techniques which are less costly to research and produce, safer, and more effective. As the once-revolutionary techniques and treatments of personalized medicine take hold, the diagnosis and treatment of disease will change forever[2][3][4][5][6].

3. Progress of Precision Medicine and Positive Outcomes

While early work in fields such as drug metabolism which laid the groundwork for precision medicine did not lead directly to better drugs or outcomes, continued advancements in technology, genetics and pharmacological knowledge and research are propelling rapid growth and change in precision medicine[6][7]. The addition of more powerful data gathering and analyses is steadily broadening the uses for genetic and genomic information. The progress in breast cancer represents our newfound ability to synthesize knowledge of patients' genetics and genomics with their tumors' markers and mutations, and in turn provide better therapies and outcomes. The benefits of this effort will spread beyond oncology to aid in battling diabetes, rheumatoid arthritis, and a host of other scourges[8][9].

Recent advances have identified a variety of mutations which, when detected, guide clinicians in their research, and providers in treatments for specific tumors or cancer types. These include ABL1 for CML and ALL; EGFR, ALK, and ROS1 for lung cancer; BRAF for melanoma; ERBB2 for breast and gastric cancer; KIT for gastrointestinal stromal tumor; PDGFRA for leukemia and MDS; PDGFRB for dermatofibrosarcoma protuberans; and BRCA1 and BRCA2 (germline) for ovarian cancer. By the same token, there are some mutations which are used to select against targeted therapy for colorectal cancer, such as KRAS, NRAS and BRAF[9].

A recent study involving 5688 individuals with non-small cell lung cancer provides a good example of the impact of precision medicine, along with the need for further advances[10]. Gene sequencing data were generated across the group, with approximately 15 percent receiving wide-ranging sequencing for approximately 30 genes, while the remainder was checked for EGFR and ALK, two mutations which have medications available. The results indicated that the one-year mortality rates for the two groups were not remarkably different, with the rate for the broader group at 41.1 percent and the two-gene group, who received treatments for their specific mutations, was at 44.4 percent. It should be noted that, as more specifically targeted drugs are developed and consequently matched with individual mutations, the differential would be expected to increase.

4. Challenges Facing Precision Medicine

As the field of precision medicine expands, researchers will be collecting, organizing and analyzing burgeoning quantities of data; more efficient database and analytical techniques will be required to utilize all of this information[11][12][13]. As this knowledge base is used to develop individual diagnostics, we must be able to properly align individuals and subgroups with the proper tests. Such precision and accuracy is also vital to clinicians conducting trials, as well as for providers to administer the best treatments. As an example, CCR5-tropic is a particular strain of HIV which is identified through the Trofile assay; the drug Selzentry® was developed to target this specific strain of HIV based on the data produced from this diagnostic tool.

As one can imagine, the price tag for discovering more and more specific genetic information, and then developing appropriate testing and treatment methods, will be a major difficulty in bringing precision medicine into widespread practice. For one example, insurance providers will require assurance that narrowly-focused diagnostic services will accurately determine specific tumors or diseases; then they will need further proof that a particular treatment regimen will be most effective in economic terms as well as patient outcome. Otherwise, precision testing and treatment will remain out of reach for the general population, only available for those who can afford the testing and treatment. As early efforts prove successful, clinicians, pharmacologists and providers will develop more rapid, reliable, and robust tools, techniques, and treatments which should serve to lower the economic impact.

Another limiting factor in bringing precision medicine into wider use is the requirement for personnel in many facets of genetics, pharmacology, and medicine to gain detailed, sophisticated expertise in the application and analysis of testing instruments and data. Even with constant and rapid advances in clinical whole-genome and whole-exome sequencing, and their associations with specific diseases, there are wide realms of uncertainty when it comes to interpreting and analyzing the masses of data being generated. For healthcare providers to fully implement precision medicine, they will require significant training in new and emerging fields, such as biochemistry and molecular genetics, so as to be able to interpret diagnostic results and then apply their data to treatment and prevention. In dealing with cancer, proteomics, genomics and metabolomic data must be integrated, then further interpreted with relation to epidemiological and clinical results. If this isn't enough, all involved will need to accurately distinguish an ever-increasing variety of biomarkers.

5. Perspectives of Precision Medicine

Precision medicine is being built on the successes of human genomic research. The time is coming, perhaps soon, when this convergence of genetics, molecular profiling and clinical data will give all involved in researching, analyzing and treating diseases the power to provide customized treatments. The major advances in genetic and biomarker testing, along with pharmacogenetics, will help avoid harmful, inefficient, and ineffective research, producing drugs and treatments which will be more precise and effective at all levels. For example, toxigenomic markers are allowing pharmaceutical researchers to improve compound screening and patient selection; these advancements can only help to avoid failed drugs earlier in the process[14][15]. Additionally, these markers will help doctors avoid prescribing certain drugs to those who would not benefit from them, or worse, react adversely. As noted earlier, the Hercep Test/trastusumab combination, combining screening for HER2 receptors with a drug targeted to fight them, offers a paradigm for future collaboration.

Continued development of research, diagnostics and treatment equipment, tools and drugs will enable the pharmaceutical industry to invest more efficiently in researching and developing successful drugs. The public will benefit as clinicians continue to develop screens for those at greater risk of diseases. As it is, over 350 genetic tests exist, though most are limited to screening for rare monogenic diseases. Naturally, researchers are expanding their efforts to detect the polygenic disorders which afflict larger populations[16][17]. As more genetic markers are found, and tests for them developed; as better equipment and precision clinical trials benefit pharmacologists and providers, outcomes will improve through more and more accurate and reliable detection and treatment of diseases at the earliest possible stage[18][19][20]. Great progress is being made in fighting cancer, for one example, as our newfound ability to discern details of RNA, DNA, metabolites and proteins provides an ever clearer and more precise picture of an individual's genetic makeup. This ability to discern, record and analyze genetic information provides the means to rapidly detect cancer and other diseases earlier and more accurately than ever before.

References

1. Saadeh, C.; Bright, D.; Rustem, D. Precision medicine in oncology pharmacy practice. Acta Med. Acad. 2019, 48, 90–104.
2. Tourneau, C.; Borcoman, E.; Kamal, M. Molecular profiling in precision medicine oncology. Nat. Med. 2019, 25, 711–712.
3. The Evolution and Clinical Impact of Diagnostic Testing. Available online: https://www.ajmc.com/insights/diagnostic-testing/the-value-of-personalized-medicine (accessed on 9 September 2020).
4. Walko, C.; Kiel, P.J.; Kolesar, J. Precision medicine in oncology: New practice models and roles for oncology pharmacists. Am. J. Health Syst. Pharm. 2016, 73, 1935–1942.
5. Deluche, E.; Onesti, E.; Andre, F. Precision medicine for metastatic breast cancer. Am. Soc. Clin. Oncol. Educ. Book 2015, 35, 1–6.
6. Reynolds, K.; Sarangi, S.; Bardia, A.; Dizon, D.S. Precision medicine and personalized breast cancer: Combination pertuzumab therapy. Pharmgenomics Pers. Med. 2014, 7, 95–105.
7. Borgiani, P.; Ciccacci, C.; Forte, V.; Sirianni, E.; Novelli, L.; Bramanti, P.; Novelli, G. CYP4F2 genetic variant (rs2108622) significantly contributes to warfarin dosing variability in the Italian population. Pharmacogenomics 2009, 10, 261–266.
8. Ahmed, S.; Zhou, Z.; Zhou, J.; Chen, S. Pharmacogenomics of drug metabolizing enzymes and transporters: Relevance to precision medicine. Genom. Proteom. Bioinform. 2016, 14, 298–313.
9. Hyman, D.M.; Taylor, B.S.; Baselga, J. Implementing genome-driven oncology. Cell 2017, 168, 584–599.

10. Riaz, F.; Presley, C.J.; Chiang, A.C.; Longtine, J.A.; Soulos, P.R.; Adelson, K.B.; Herbst, R.S.; Nussbaum, N.C.; Sorg, R.A.; Abernethy, A.P.; et al. Disparities in broad-based genomic sequencing for patients with advanced non-small cell lung cancer. J. Geriatr. Oncol. 2019, 10, 669–672.
11. Duffy, D.J. Problems, challenges and promises: Perspectives on precision medicine. Brief. Bioinform. 2016, 17, 494–504.
12. Xue, Y.; Lameijer, E.; Ye, K.; Zhang, K.; Chang, S.; Wang, X.; Wu, J.; Gao, G.; Zhao, F.; Jian, L.; et al. Precision medicine: What challenges are we facing? Genom. Proteom. Bioinform. 2016, 14, 253–261.
13. Liu, X.; Luo, X.; Jiang, C.; Zhao, H. Difficulties and challenges in the development of precision medicine. Clin. Genet. 2019, 95, 569–574.
14. Morris-Rosendahl, D.J. The future of genetic testing for drug response. Dialogues Clin. Neurosci. 2004, 6, 27–37.
15. Ginsburg, G.S.; Willard, H.F. Genomic and personalized medicine: Foundations and applications. Translational Research. J. Lab. Clin. Med. 2009, 154, 277–287.
16. Beger, R.D. A review of applications of metabolomics in cancer. Metabolites 2013, 3, 552–574.
17. Pennie, W.D.; Tugwood, J.D.; Oliver, G.J.A.; Kimber, I. The principles and practice of toxicogenomics: Applications and opportunities. Toxicol. Sci. 2000, 54, 277–283.
18. Sutherland, J.J.; Webster, Y.W.; Willy, J.A.; Searfoss, G.H.; Goldstein, K.M.; Irizarry, A.R.; Hall, D.G.; Stevens, J.L. Toxicogenomic module associations with pathogenesis: A network-based approach to understanding drug toxicity. Pharm. J. 2018, 18, 377–390.
19. Liu, A.; Huang, R.; Roberts, R.; Tong, W. Toxicogenomics: A 2020 Vision. Trends Pharm. Sci. 2019, 40, 92–103.
20. McCarroll, S.A.; Hyman, S.E. Progress in the genetics of polygenic brain disorders: Significant new challenges for neurobiology. Neuron 2013, 80, 578–587.
