MOLECULAR HEALTH

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Catalogue of
peer-reviewed studies

2009 – 2024

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Peer-reviewed studies 2009-2024

Over the past decade and a half, Molecular Health has adopted an open innovation policy. This has resulted in successful collaborations with some of the world's most renowned biomedical institutes and innovators. Together, we have tackled some of the most significant healthcare challenges, with Molecular Health providing the backbone of clinico-molecular data and cutting-edge analytical strategies.

These diverse projects have included improving the detection and prediction of safety concerns for new and approved drugs, as well as applying genome-guided treatment decision support for cancer patients in clinical trial contexts. This work has led to the development of novel computational approaches for drug repositioning and the rational design of drug combinations, as well as the discovery of new predictive biomarkers.

Although this work has been presented at globally renowned conferences such as ASCO, AACR, ESMO, ACMG, PMWC and Bio-IT, in this section we provide details of peer-reviewed submissions that have been successfully published in journals such as Cancer Cell, Proceedings of the National Academy of Sciences, Nature Communications and Nature Reviews in Clinical Oncology. For each paper, we provide not only the abstract and references but also details of the specific collaboration partner (if involved) and the analytical technology used.

About Molecular Health

Molecular Health is a leader in precision medicine. The company's proprietary Dataome technology integrates and contextualizes clinical, molecular, and pharmaceutical data to provide a profound understanding of the etiology of health and disease conditions. Molecular Health's IVDR-certified software product, MH Guide, provides laboratories and healthcare providers with molecular-based diagnostics and clinical decision support. Molecular Health offers Dataome-based solutions to improve clinical trial design, drug target identification and validation, as well as indication and biomarker finding for biopharmaceutical companies.

Molecular Health Technologies
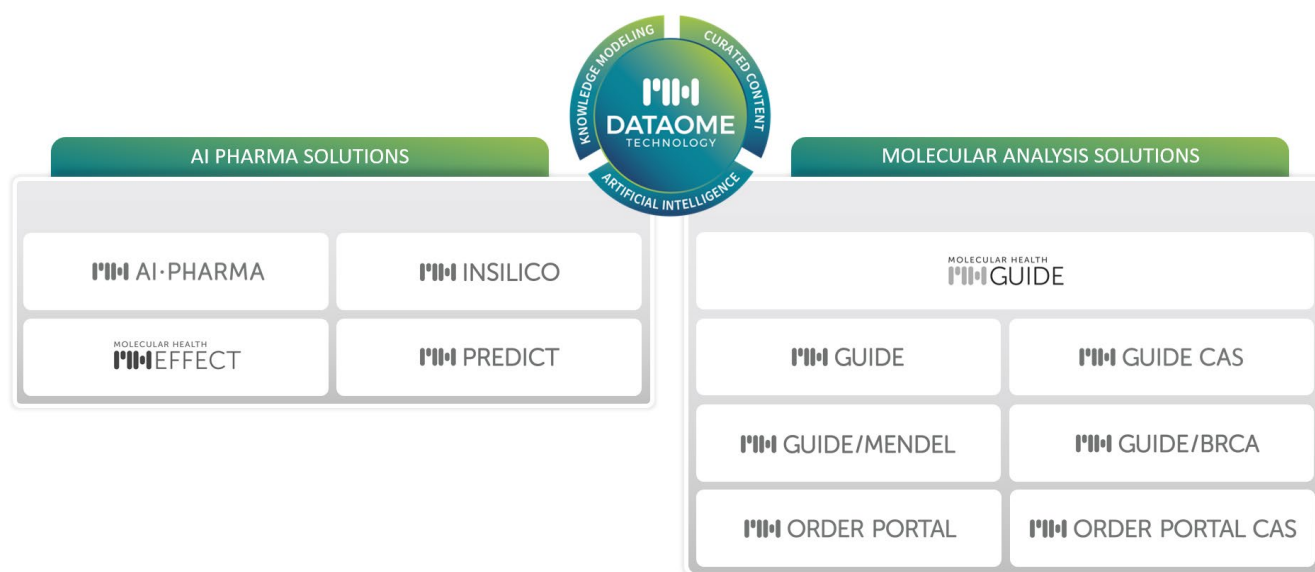
* CE marked IVD software MH Guide available in the EU. ** MH Guide CAS is offered as Research Use Only (RUO) product by MH's global strategic partner Integrated DNA Technologies (IDT) outside of the EU.

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Highlight

Novel approach to drug repositioning / combination therapy design

Src activation by β-adrenoreceptors is a key switch for tumour metastasis.

What was the current knowledge on the topic prior to this work?

Clinical and animal studies support the notion that psychological factors such as stress, chronic depression, and lack of social support might promote tumor growth and progression. The molecular mechanisms responsible for these effects were up to this time largely unknown.

What question did this study address?

Previous work determined that sympathetic nervous system activity can directly enhance the pathogenesis of ovarian carcinoma by protecting tumor cells from anoikis, promoting tumor cell invasion and tumor-associated angiogenesis. We found that these effects were mediated through activation of tumor cell ADRB2 (Adrenergic Receptor), but its downstream signaling pathways were not well understood. This study sought to characterize these mechanisms.

What did this study add to our knowledge?

In this study, we used the Dataome Knowledgebase to predict a signalling network downstream of ADRB. Subsequent laboratory -ased validation demonstrated that ADRB signaling leads to Src activation by a unique PKA-mediated mechanism, which is critical to the regulation of phosphoproteomic networks associated with ovarian cancer progression.

How might this change drug discovery, development, and/or therapeutics?

On the basis of our work, beta-antagonists were shown to abrogate many of the deleterious effects of increased adrenergic signaling in response to bio-behavioral stress. The findings supported the use of Src family kinase inhibitors as tools to block the deleterious effects of increased sympathetic activity. Collectively, the data represented a new understanding of Src regulation in response to adrenergic signaling in cancer cells and provided a biologically plausible and potent way of inhibiting tumor progression among cancer patients.

Journal

nature **COMMUNICATIONS**

Reference

2013

Collaborator

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Technology

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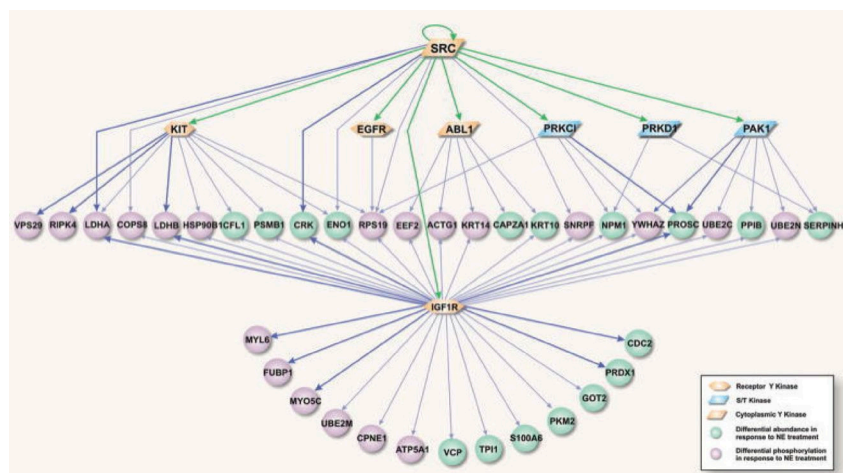

Figure Legend. Putative phosphorylation cascade triggered by the NE-induced activation of Src

Here we used the Dataome Knowledgebase to predict a signalling network downstream of SRC in response to ADRB2 activation by Norepinephrine (NE).

For more information, see abstract number 14.

Discovery of a novel predictive biomarker

Erythropoietin stimulates tumor growth via ephB4.

What was the current knowledge on the topic prior to this work?

Recombinant human Erythropoietin (rhEpo) was commonly prescribed to treat chemotherapy induced anemia in cancer patients. Many retrospective studies suggested poorer overall survival and progression free survival in response to rhEpo treatment. Available evidence suggested that the EPO receptor was not responsible for these effects, leading us to hypothesize the existence of a novel EPO receptor.

What question did this study address?

Recombinant human Erythropoietin (rhEpo) was commonly prescribed to treat chemotherapy induced anemia in cancer patients. Many retrospective studies suggested poorer overall survival and progression free survival in response to rhEpo treatment. Available evidence suggested that the EPO receptor was not responsible for these effects, leading us to hypothesize the existence of a novel EPO receptor.

What did this study add to our knowledge?

In this study, we identified a new mechanism that EphB4 acts as a critical mediator of erythropoietin signaling, which can induce tumor progression in cancer patients. Altogether our study provided a novel and clinically significant dimension to the biology of erythropoietin, which was not appreciated before.

How might this change drug discovery, development, and/or therapeutics?

The discovery resulted in a novel predictive biomarker for identifying patients who were more likely to experience poorer outcomes in response to rhEPO treatment (i.e. by virtue of high EPHB4 expression) and therefore be excluded from receiving this therapy. In addition, it also emphasized the relevance of EphB4 as an anticancer target and opened up the opportunity for a number of rational combination approaches with existing drugs (e.g. dasatinib).
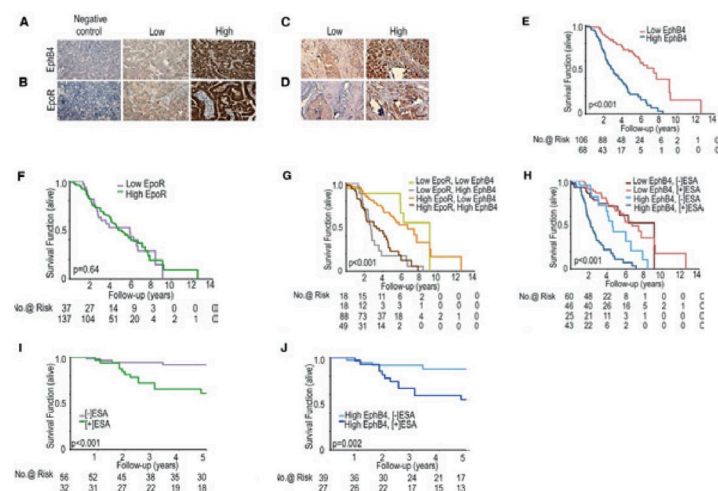

Figure: Clinical Relevance of EphB4 and EpoR Expression and ESA Treatment in Cancer Patients. (A–D) Representative immunohistochemical peroxidase staining for (A) EphB4 and (B) EpoR expression in ovarian cancer and (C) EphB4 and (D) EpoR expression in breast cancer samples.(E–G) Kaplan-Meier curves of diseasespecific mortality for ovarian (E–H) and breast (I and J) cancer patients stratified by tumoral expression of (E) EphB4, (F) EpoR, or (G) both EphB4 and EpoR. (H) Evaluation of disease-specific survival duration of ovarian cancer patients based on ESA treatment and EphB4 expression. (I) Disease-specific survival analysis of breast cancer patients stratified by ESA treatment. (J) Disease-specific survival of breast cancer patients based on ESA treatment and EphB4 expression. The scale bar represents 50 μm.
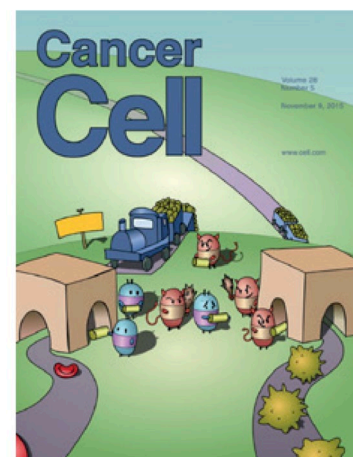
We received Cancer Cell. The associated description is as follows "On the cover: Recombinant human erythropoietin (rhEpo, green bricks) has been used to relieve chemotherapy-induced anemia (left path; red blood cells shown in red). The possibility that rhEpo may promote tumor growth has been suggested, but the underlying mechanisms are not well understood. Pradeep et al. (pp. 610–622) identify EphB4 (red horned characters) as an alternative to the traditional erythropoietin receptor (EpoR; blue characters). Interaction of rhEpo and EphB4 triggers STAT3 signaling and promotes tumor growth and progression (right path; tumor shown in green).

Genome guided treatment decision support using MH Guide

Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer.

What was the current knowledge on the topic prior to this work?

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancerrelated mortality in the USA and Europe and is predicted to become the second by 2030. The lack of treatment response to conventional therapeutic approaches as radiation and chemotherapy is attributable to many factors, including extrinsic or intrinsic resistance.

What question did this study address?

Pancreatic cancers may benefit from the developments in precision medicine, which has proven worthy elsewhere. In the present study, we aimed to investigate the clinical applicability of using NGS in combination with MH Guide to generate individualized analysis for a personalized approach for the treatment of pancreatic cancer.

What did this study add to our knowledge?

We demonstrated that NGS data in combination with evidence-based software analysis using MH Guide is feasible in the clinical setting of pancreatic cancer: unraveling novel treatment options and indicating important biomarkers of increased toxicity.

How might this change drug discovery, development, and/or therapeutics?

Results from this study provided the clinical rationale for the design of follow-on clinical studies (e.g. the PePaCaKa trial) designed to demonstrate the clinical utility of MH Guide in supporting treatment decision making for PDAC patients.

Journal

Molecular Oncology

Reference

2017

Collaborator

Karolinska Institutet

Technology

MH GUIDE

Highlight

Prediction of drug safety label evolution using MH Effect

Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities.

What was the current knowledge on the topic prior to this work?

Predictive safety in the post-market setting at the FDA has relied upon expert review of available evidence from case reports, medical records, FAERS, and the literature. Systemic, quantitative methods were being evaluated.
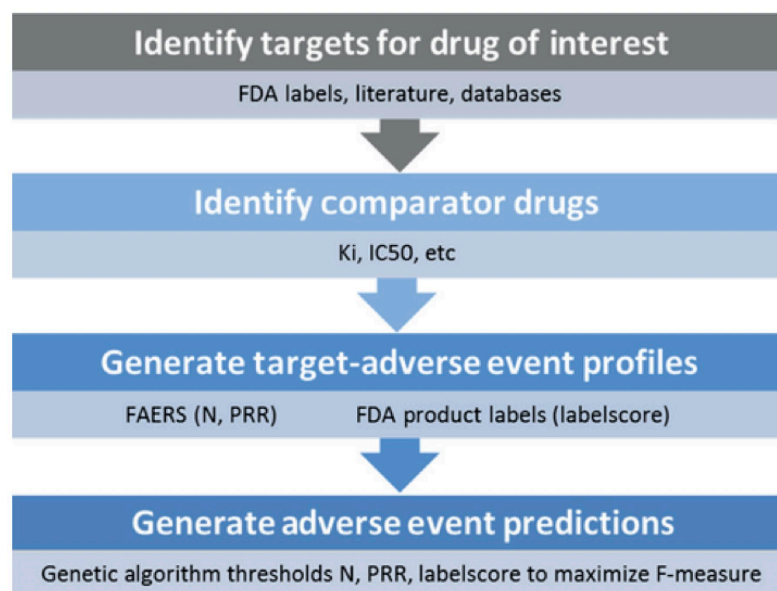
What question did this study address?

We asked whether Target Adverse Event (TAE) profiles might improve the prediction of drug safety labels. The MH Effect technology provides TAE's i.e. aggregated drug AEs at the level of shared pharmacological targets. The study assessed the use of TAE profiles in anticipating significant postmarket drug AEs of interest.

What did this study add to our knowledge?

This study confirmed that aggregating AEs by pharmacological targets is predictive of postmarket AEs.

How might this change drug discovery, development, and/or therapeutics?

In addition to assisting with postmarket pharmacovigilance, this approach may also be used to anticipate AEs that may occur during drug development.

Journal

CPT: Pharmacometrics & Systems Pharmacology

Collaborator

US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

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Identify targets for drug of interest
FDA labels, literature, databases

Identify comparator drugs
Ki, IC50, etc

Generate target-adverse event profiles
FAERS (N, PRR)   FDA product labels (labelscore)

Generate adverse event predictions
Genetic algorithm thresholds N, PRR, labelscore to maximize F-measure

Showing the workflow for drug label prediction. MH Effect permitted the automated generation of Target Adverse Event profiles, a key element of this predictive workflow.

1. Clinical and economic impact of the non-responder phenomenon-implications for systems based discovery.

Molecular diversity is a hallmark of life. Unfortunately, given that the clinical benefit of a drug can only be realized under certain genetic/molecular conditions, such heterogeneity can mean the difference between survival and death. For most targeted therapies it appears that such conditions are met in only a small percentage of patients, particularly in the monotherapy context. Notwithstanding, the nonresponder phenomenon can be viewed as a low-hanging fruit among medical needs, with a large body of scientific knowledge surrounding the target
and the diseased system.

This knowledge, together with information about the molecular sources of nonresponse, provides a rational framework upon which novel intervention strategies can be built. Driven by such molecular considerations and the enormous economic implications, new levels of innovation are urgently required. Systems level patient characterization coupled with innovative in silico strategies hold great promise and suggest a future of theranostic-linked combination therapies, optimized cohort selection and rational prioritization of clinical opportunities.

2. Molecular perspectives on the non-responder phenomenon.

With the advent of targeted therapies promising to revolutionise the nature and success of patient care, the field of clinical oncology is facing a highly exciting future. While much of this enthusiasm comes from the hope for improved patient outcomes, a review of clinical response/relapse rates for current therapies provides a more sobering perspective. Given that the majority of patients are intrinsically resistant to the therapeutic potential of these molecules, efforts are now directed at characterising such non responsive system behaviour and causative molecular insults.

Testament to this is an expanding catalogue of target and system-based aberrations, often defined through retrospective analyses of clinical tissue and associated outcome data. What has emerged is a complex picture, where numerous potential sources of cancer-specific aberration can contribute to refractory tumour behaviour. Clinicians, regulators and sponsors must now collaborate to determine how such knowledge should be used to enhance the clinical decision process and associated regulatory guidance.

3. Serum-based microRNAs: are we blinded by potential?

In a recent issue of PNAS, Mitchell et al. (1) reported exciting insights into the use of circulating microRNAs as biomarkers for cancer detection. Recently corroborated by similar studies, the potential now appears to extend well beyond the clinical oncology domain (2, 3). The observed specificity and simplicity of the approach are particularly striking and suggest that serumbased microRNAs could emerge as revolutionary sources of biomarker information. However, in the absence of thorough functional knowledge, might our focus on diagnostic potential be to the detriment of novel therapeutic opportunity?

The diagnostic specificity of circulating microRNAs supports the contention that they are not the molecular remnants of once-living tumor cells, but rather of utmost functional importance. This is consistent with the roles of other established biomarkers such as BCR-ABL or HER2, which further exemplify that modulation of "biomarker" function can produce efficacious therapeutic effects. Such perspective will no doubt encourage further hypotheses and experimentation, but perhaps one important speculation warrants immediate investigation. Might the secretion of specific microRNAs in cancer patients be a critical component of a tumor's molecular armamentarium? By affecting cellular systems elsewhere in the body, could the goal of such molecules be to produce a systemic environment that is conducive to disease progression? If true, such a mechanism would open an exciting therapeutic strategy involving the serum-based exchange of cancer-associated microRNAs for a healthy canonical complement. Not unlike the therapeutic premise of enzyme-replacement therapy, the concept should warrant immediate exploration by the microRNA community.

Journal

PNAS

Reference

Proc Natl Acad Sci U S A. 2009;106(1):E5
PMID: 19106287

2009

Collaborator

MOLECULAR HEALTH

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GUIDE

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4. Drug profiling: knowing where it hits.

Off-target hits of drugs can lead to serious adverse effects or, conversely, to unforeseen alternative medical utility. Selectivity profiling against large panels of potential targets is essential for the drug discovery process to minimize attrition and maximize therapeutic utility. Lately, it has become apparent that drug promiscuity (polypharmacology) goes well beyond target families; therefore, lowering the profiling costs and expanding the coverage of targets is an industry-wide challenge to improve predictions. Here, we review current and promising drug profiling alternatives and commercial solutions in these exciting emerging fields.

Journal

DRUG DISCOVERY TODAY

Reference

Drug Discov Today. 2010;15(17-18):749-56.

2010

Collaborator

UCD DUBLIN

Technology

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5. LAITOR - Literature assistant for identification of terms co-occurrences and relationships.

Biological knowledge is represented in scientific literature that often describes the function of genes/proteins (bioentities) in terms of their interactions (biointeractions). Such bioentities are often related to biological concepts of interest that are specific of a determined research field. Therefore, the study of the current literature about a selected topic deposited in public databases, facilitates the generation of novel hypotheses associating a set of bioentities to a common context.

We created a text mining system (LAITOR: Literature Assistant for Identification of Terms co-Occurrences and Relationships) that analyses co-occurrences of bioentities, biointeractions, and other biological terms in MEDLINE abstracts. The method accounts for the position of the co-occurring terms within sentences or abstracts. The system detected abstracts mentioning protein-protein interactions in a standard test (BioCreative II IAS test data) with a precision of 0.82-0.89 and a recall of 0.48-0.70. We illustrate the application of LAITOR to the detection of plant response genes in a dataset of 1000 abstracts relevant to the topic. Text mining tools combining the extraction of interacting bioentities and biological concepts with network displays can be helpful in developing reasonable hypotheses in different scientific backgrounds.

Journal

BMC

Reference

BMC Bioinformatics. 2010;11:70.
PMID:20122157

2010

Collaborator

MDC MAX DELBRÜCK CENTER
FOR MOLECULAR MEDICINE
IN THE HELMHOLTZ ASSOCIATION

Technology

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6. EMT is the dominant program in human colon cancer.

Colon cancer has been classically described by clinicopathologic features that permit the prediction of outcome only after surgical resection and staging. We performed an unsupervised analysis of microarray data from 326 colon cancers to identify the first principal component (PC1) of the most variable set of genes. PC1 deciphered two primary, intrinsic molecular subtypes of colon cancer that predicted disease progression and recurrence.

Here we report that the most dominant pattern of intrinsic gene expression in colon cancer (PC1) was tightly correlated (Pearson R = 0.92, P < 10(-135)) with the EMT signature— both in gene identity and directionality. In a global micro-RNA screen, we further identified the most anti-correlated microRNA with PC1 as MiR200, known to regulate EMT. These data demonstrate that the biology underpinning the native, molecular classification of human colon cancer-- previously thought to be highly heterogeneous-- was clarified through the lens of comprehensive transcriptome analysis.

Journal

BMC

Reference

BMC Med Genomics. 2011;4:9.
PMID: 21251323

2011

Collaborator

MOFFITT
CANCER CENTER

Technology

GUIDE

7. Genetic determinants of anticancer drug activity: towards a global approach to personalized cancer medicine.

While current trials of anticancer agents serve to provide a population-based validation of therapeutic activity, clinical success is typically restricted to tumors of select molecular subtype. Recent insights have yielded a growing catalogue of germline and tumor-based aberrations that can predetermine whether a patient will achieve clinical benefit from a drug or not.

Thus, in order to realize the true potential of anticancer agents, we need to define the molecular contexts under which they will prove both efficacious and safe. In this article, we provide an overview of such molecular determinants and introduce the concept of 'cancer patient profiling' - the process and science of defining the optimal therapy for a given patient through the generation and analysis of system-wide molecular information.

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8. Intelligent clinical decision support systems for non-invasive bladder cancer diagnosis.

Currently, there are some paradigm shifts in medicine, from the search for a single ideal biomarker, to the search for panels of molecules, and from a reductionistic to a systemic view, placing these molecules on functional networks. There is also a general trend to favor noninvasive biomarkers. Identifying non-invasive biomarkers in high- throughput data, having thousands of features and only tens of samples is not trivial.

Here, we proposed a methodology and the related concepts to develop intelligent molecular biomarkers, via knowledge discovery in data, illustrated on bladder cancer diagno- sis. A knowledge discovery in data approach, with computational intelligence methods, is used to identify the relevant features and discover their relationships with the diagno- sis. The intelligent non-invasive diagnosis systems, is based on a team of mathematical models, discovered with genetic programming, and taking as inputs plasma microRNA.

This systems share with other intelligent systems we build, using this methodology but different computational/artificial intelligence techniques and clinical situations— chronic hepatitis, bladder cancer progression, and prostate cancer—the best published accuracy, even 100%. Computational intelligence could be a strong foundation for the newly emerging Knowledge-Based-Medicine. The impact of this paradigm shift on medical practice could be enormous. Instead of offering just hints or evidences to the clinicians, like Evidence-Based-Medicine, Knowledge-Based-Medicine which is made possible and co-exists with Evidence- Based-Medicine, offers intelligent clinical deci- sion supports systems.

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9. Personalized cancer medicine-advances and socio-economic challenges.

It was Hippocrates, the father of Western medicine, who first emphasized the patient as the most important determinant of therapeutic efficacy. Although the principle of adjusting treatment to specific patient characteristics has since been the strategy of physicians, this is undermined by a population-biased approach to drug development.

Therefore, it is generally true to say that our current evidential approach to cancer treatment is driven more by drug-regulation requirements and market considerations than the specific needs of an individual patient. But, with cancer drug costs now spiraling out of control and the modest efficacy typically seen in patients, the community is again turning to Hippocrates' ancient paradigm-- this time with emphasis on molecular considerations. Rapidly evolving technologies are empowering us to describe the molecular 'nature' of a patient and/or tumor and with this has come the beginning of truly personalized medicine, with maximized efficacy, cost effectiveness and hopefully improved survival for the patient.

Journal

nature REVIEWS CLINICAL ONCOLOGY

Reference

Nat Rev Clin Oncol. 2011;8(12):735-41.
PMID: 21989071

2011

Collaborator

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10. Using graph theory to analyze biological networks.

Understanding complex systems often requires a bottom-up analysis towards a systems biology approach. The need to investigate a system, not only as individual components but as a whole, emerges. This can be done by examining the elementary constituents individually and then how these are connected. The myriad components of a system and their interactions are best characterized as networks and they are mainly represented as graphs where thousands of nodes are connected with thousands of vertices.

In this article we demonstrate approaches, models and methods from the graph theory universe and we discuss ways in which they can be used to reveal hidden properties and features of a network. This network profiling combined with knowledge extraction will help us to better understand the biological significance of the system.

Journal

BMC

BioData Mining

Reference

BioData Min. 2011;4:10
PMID:21527005

2011

Collaborator

Technology

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11. A scatter-based prototype framework and multi-class extension of support vector machines.

We provide a novel interpretation of the dual of support vector machines (SVMs) in terms of scatter with respect to class prototypes and their mean. As a key contribution, we extend this framework to multiple classes, providing a new joint Scatter SVM algorithm, at the level of ist binary counterpart in the number of optimization variables.

This enables us to implement computationally efficient solvers based on sequential minimal and chunking optimization. As a further contribution, the primal problem formulation is developed in terms of regularized risk minimization and the hinge loss, revealing the score function to be used in the actual classification of test patterns. We investigate Scatter SVM properties related to generalization ability, computational efficiency, sparsity and sensitivity maps, and report promising results.

12. Biggest challenges in bioinformatics.

The third Heidelberg Unseminars in Bioinformatics (HUB) was held on 18th October 2012, at Heidelberg University, Germany. HUB brought together around 40 bioinformaticians from academia and industry to discuss the 'Biggest Challenges in Bioinformatics' in a 'World Caf.' style event.

13. Systemic microRNA measurement, a useful tool for predicting diagnosis in bladder cancer.

Bladder cancer (BC) is a burdensome disease with significant morbidity, mortality, and cost. The development of novel plasma-based biomarkers for BC diagnosis and surveillance could significantly improve clinical outcomes and decrease health expenditures. Plasma miRNAs are promising biomarkers that have yet to be rigorously investigated in BC. To determine the feasibility and efficacy of detecting BC with plasma miRNA signatures. Plasma miRNA was isolated from 20 patients with bladder cancer and 18 noncancerous controls.

Samples were analyzed with a miRNA array containing duplicate probes for each miRNA in. the Sanger database. Logistic regression modeling was used to optimize diagnostic miRNA signatures to distinguish between muscle invasive BC (MIBC), non-muscle-invasive BC (NMIBC) and noncancerous controls. Seventy-nine differentially expressed plasma miRNAs (local false,discovery rate [FDR] <0.5) in patients with or without BC were identified. Some diagnostically relevant miRNAs, such as miR-200b, were up-regulated in MIBC patients, whereas others, such as miR-92 and miR-33, were inversely correlated with advanced clinical stage, supporting the notion that miRNAs released in the circulation have a variety of cellular origins.

Logistic regression modeling was able to predict diagnosis with 89% accuracy for detecting the presence or absence of BC, 92% accuracy for distinguishing invasive BC from other cases, 100% accuracy for distinguishing MIBC from controls, and 79% accuracy for three-way classification between MIBC, NIMBC, and controls.

This study provides preliminary data supporting the use of plasma miRNAs as a noninvasive means of BC detection. Future studies will be required to further specify the optimal plasma miRNA signature, and to apply these signatures to clinical scenarios, such as initial BC detection and BC surveillance.

14. Src activation by β-adrenoreceptors is a key switch for tumour metastasis.

Noradrenaline can modulate multiple cellular functions important for cancer progression; however, how this single extracellular signal regulates such a broad array of cellular processes is unknown. Here we identify Src as a key regulator of phosphoproteomic signalling networks activated in response to beta-adrenergic signalling in cancer cells.

These results also identify a new mechanism of Src phosphorylation that mediates beta-adrenergic/PKA regulation of downstream networks, thereby enhancing tumour cell migration, invasion and growth. In human ovarian cancer samples, high tumoural noradrenaline levels were correlated with high pSrc(Y419) levels. Moreover, among cancer patients, the use of beta blockers was significantly associated with reduced cancer-related mortality. Collectively, these data provide a pivotal molecular target for disrupting neural signalling in the tumour microenvironment.

15. Drugs highly associated with Infusion reactions reported using two different data-mining methodologies.

Infusion reactions can be serious life threatening adverse events and have been associated with many drugs and biologic agents. Our objective was to report drugs associated with infusion reactions using two different data-mining methodologies.

The Food and Drug Administration Adverse Event Reporting System (FAERS) was data-mined for drugs highly associated with infusion reactions. Drugs were included if there were >10 reported adverse events and if the Empirical Bayesian Geometric Mean (EBGM) score ≥ 2. Molecular Health's MASE (Molecular Analysis of Side Effects) reports Proportional Reporting
Ratios (PRR) for drugs highly associated with infusion reactions and was cross-referenced to improve detection sensitivity.

Using FAERS, the highest EBGM scores by class were reported as: pegloticase and α-1-antitrypsyn (enzymes), iron dextran and ferric gluconate (electrolytes and nutrients), infliximab and gemtuzumab (immunomodulators), and paclitaxel and oxaliplatin (antimetabolites). Using MASE, the highest PRR scores were reported as: idursulfase and galsulfase (enzymes), iron dextran and phytonadione (electolytes and nutrients), gemtuzumab and infliximab
(immunomodulators), mercaptopurine and azathioprine (antimetabolites). Amphotericin and vancomycin had the highest scores for the antimicrobial class for both FAERS and MASE. Using the two statistical methods EBGM and PRR, both specificity and sensitivity were preserved.

However, neither system detected several drugs with established relationships to infusion reactions, including protamine and nitroglycerine. Reactions caused by these drugs were possibly underreported because the effects have been well established or due to evolution of administration with slower administration. We hope this analysis encourages further research into overlapping mechanisms for infusion reactions.

16. Data mining FAERS to analyse molecular targets highly associated with Stevens Johnson Syndromes.

Drug features that are associated with Stevens-Johnson syndrome (SJS) have not been fully characterized. A molecular target analysis of the drugs associated with SJS in the FDA Adverse Event Reporting System (FAERS) may contribute to mechanistic insights into SJS pathophysiology. The publicly available version of FAERS was analyzed to identify disproportionality among the molecular targets, metabolizing enzymes, and transporters for drugs associated with SJS.

The FAERS in-house version was also analyzed for an internal comparison of the drugs most highly associated with SJS. Cyclooxygenases 1 and 2, carbonic anhydrase 2, and sodium channel 2 alpha were identified as disproportionately associated with SJS. Cytochrome P450 (CYPs) 3A4 and 2C9 are disproportionately represented as metabolizing enzymes of the drugs associated with SJS adverse event reports. Multidrug resistance protein 1 (MRP-1), organic anion transporter 1 (OAT1), and PEPT2 were also identified and are highly associated with the transport of these drugs.

A detailed review of the molecular targets identifies important roles for these targets in immune response. The association with CYP metabolizing enzymes suggests that reactive metabolites and oxidative stress may have a contributory role. Drug transporters may enhance intracellular tissue concentrations and also have vital physiologic roles that impact keratinocyte proliferation and survival. Data mining FAERS may be used to hypothesize mechanisms for adverse drug events by identifying molecular targets that are highly associated with drug-induced adverse events. The information gained may contribute to systems biology disease models.

17. How to learn about gene function: text-mining or ontologies?

As the amount of genome information increases rapidly, there is a correspondingly greater need for methods that provide accurate and automated annotation of gene function. For example, many high-throughput technologies--e.g., next-generation sequencing--are being used today to generate lists of genes associated with specific conditions. However, their functional interpretation remains a challenge and many tools exist trying to characterize the function of gene-lists. Such systems rely typically in enrichment analysis and aim to give a quick insight into the underlying biology by presenting it in a form of a summary-report.

While the load of annotation may be alleviated by such computational approaches, the main challenge in modern annotation remains to develop a systems form of analysis in which a pipeline can effectively analyze gene-lists quickly and identify aggregated annotations through computerized resources. In this article we survey some of the many such tools and methods that have been developed to automatically interpret the biological functions underlying gene-lists. We overview current functional annotation aspects from the perspective of their epistemology (i.e., the underlying theories used to organize information about gene function into a body of verified and documented knowledge) and find that most of the currently used functional annotation methods fall broadly into one of two categories: they are based either on 'known' formally-structured ontology annotations created by 'experts' (e.g., the GO terms used to describe the function of Entrez Gene entries), or--perhaps more adventurously—on annotations inferred from literature (e.g., many text-mining methods use computer-aided reasoning to acquire knowledge represented in natural languages).

Overall however, deriving detailed and accurate insight from such gene lists remains a challenging task, and improved methods are called for. In particular, future methods need to (1) provide more holistic insight into the underlying molecular systems; (2) provide better follow-up experimental testing and treatment options, and (3) better manage gene lists derived from organisms that are not well-studied. We discuss some promising approaches that may help achieve these advances, especially the use of extended dictionaries of biomedical concepts and molecular mechanisms, as well as greater use of annotation benchmarks.

18. Relationships of clinical response to relevant molecular signal during Phase I testing of Aurora Kinase A inhibitor: Retrospective assessment.

Retrospective analysis utilizing "next generation sequencing (NGS)" was done on cancer tissue harvested from 14 patients prior to receiving MLN8237, a novel Aurora Kinase A inhibitor. The responding patients (n=4) were characterized by stable disease ≥6 months and prolonged time of progression (≥1.3 fold prior treatment). Differential patterns of nodal connectivity in proteinprotein interaction networks (consequent to determined genomic alterations) emerged from the comparison between responder and non-responder groups.

The responding patient population showed high connectivity within MYC related genes including regulators of the Wnt/beta-catenin pathway. On the other hand, the non-responding patients showed high connectivity centered on the TP53/RB1 axis. Matching "targeted therapy to target" is a sine qua non for maximizing effective therapy in appropriate patients and NGS mapping may further our understanding of the relationships between molecular biological pathways and targeted therapy response.

While awaiting further progress in systems analysis across "omic" levels (genomictranscriptomic-proteomic), research involving of NGS sequence mapping to interrogate patient response to therapy in order to help elucidate molecular therapeutic predictors is justified based on the urgent needs of patient care.

19. Erythropoietin Stimulates Tumor Growth via EphB4.

While recombinant human erythropoietin (rhEpo) has been widely used to treat anemia in cancer patients, concerns about its adverse effects on patient survival have emerged. A lack of correlation between expression of the canonical EpoR and rhEpo's effects on cancer cells prompted us to consider the existence of an alternative Epo receptor. Here, we identified EphB4 as an Epo receptor that triggers downstream signaling via STAT3 and promotes rhEpo-induced tumor growth and progression.

In human ovarian and breast cancer samples, expression of EphB4 rather than the canonical EpoR correlated with decreased disease-specific survival in rhEpo-treated patients. These results identify EphB4 as a critical mediator of erythropoietin-induced tumor progression and further provide clinically significant dimension to the biology of erythropoietin.

Journal

Cancer Cell

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20. Improving drug safety with a systems pharmacology approach.

Systems pharmacology is used to mechanistically analyze drug-adverse drug reaction (ADRs) pairs and is a promising solution to the complex problem of understanding mechanisms of toxicity. In this research, we have explored the feasibility of retrospectively mapping population-level adverse events from the FDA Adverse Event Reporting System (FAERS) to chemical and biological databases to identify drug safety signals and the underlying molecular mechanisms. We used an analytic platform - Molecular Analysis of Side Effects (MASE™).

For this purpose, we selected the adverse event of severe and potentially fatal cutaneous reactions (SCARs) that are associated with acetaminophen (APAP). SCARs encompass the continuum between Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). We found a statistically significant association between APAP and TEN, the most severe form of SCARs. We also explored the influence of APAP on other classes of drugs commonly associated with SCARs. We found that APAP significantly reduced the risk of SCARs commonly associated with carbamazepine (CBZ).

We used molecular docking simulations to propose a mechanism for APAP's reduction in CBZ-induced SCARs which is competitive inhibition of the binding of CBZ to HLA-B*15:02. We conclude that systems pharmacology can complement established surveillance methodologies by providing a means to undertake an independent investigation and review of the mechanisms by which drugs cause adverse events.

Journal

European Journal of
PHARMACEUTICAL
SCIENCES

Collaborator

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Technology

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21. Use of "big data" in drug discovery and clinical trials.

Oncology is undergoing a data-driven metamorphosis. Armed with new and ever more efficient molecular and information technologies, we have entered an era where data is helping us spearhead the fight against cancer. This technology driven data explosion, often referred to as "big data", is not only expediting biomedical discovery, but it is also rapidly transforming the practice of oncology into an information science.
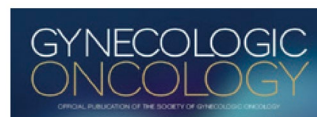
This evolution is critical, as results to-date have revealed the immense complexity and genetic heterogeneity of patients and their tumors, a sobering reminder of the challenge facing every patient and their oncologist. This can only be addressed through development of clinico-molecular data analytics that provide a deeper understanding of the mechanisms controlling the biological and clinical response to available therapeutic options. Beyond the exciting implications for improved patient care, such advancements in predictive and evidence-based analytics stand to profoundly affect the processes of cancer drug discovery and associated clinical trials.

Journal

GYNECOLOGIC ONCOLOGY

OFFICIAL PUBLICATION OF THE SOCIETY OF GYNECOLOGIC ONCOLOGY

Reference

Gynecol Oncol. 2016;141(1):17-23.
PMID: 27016224

2016

Collaborator

MOLECULAR HEALTH

Technology

GUIDE

22. A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC.

Colorectal cancer (CRC) is a highly heterogeneous disease, for which prognosis has been relegated to clinicopathologic staging for decades. There is a need to stratify subpopulations of CRC on a molecular basis to better predict outcome and assign therapies.

Here we report targeted exome-sequencing of 1,321 cancer-related genes on 468 tumour specimens, which identified a subset of 17 genes that best classify CRC, with APC playing a central role in predicting overall survival. APC may assume 0, 1 or 2 truncating mutations, each with a striking differential impact on survival. Tumours lacking any APC mutation carry a worse prognosis than single APC mutation tumours; however, two APC mutation tumours with mutant KRAS and TP53 confer the poorest survival among all the subgroups examined. Our study demonstrates a prognostic role for APC and suggests that sequencing of APC may have clinical utility in the routine staging and potential therapeutic assignment for CRC.

Journal

nature COMMUNICATIONS

Reference

Nat. Commun. 7, 11743.
doi:10.1038/ncomms11743
PMID: 27302369

2016

Collaborator

Gibbs Cancer Center & Research Institute

Technology

GUIDE

23. Reliability of algorithmic somatic copy number alteration detection from targeted capture data.

Whole exome and gene panel sequencing are increasingly used for oncological diagnostics. To investigate the accuracy of SCNA detection algorithms on simulated and clinical tumor samples, the precision and sensitivity of four SCNA callers were measured using 50 simulated whole exome and 50 simulated targeted gene panel datasets, and using 119 TCGA tumor samples for which SNP array data were available. On synthetic exome and panel data, VarScan2 mostly called false positives, whereas Control-FREEC was precise (>90% correct calls) at the cost of low sensitivity (<40% detected). ONCOCNV was slightly less precise on gene panel data, with similarly low sensitivity.

This could be explained by low sensitivity for amplifications and high precision for deletions. Surprisingly, these results were not strongly affected by moderate tumor impurities; only contaminations with more than 60% non-cancerous cells resulted in strongly declining precision and sensitivity. On the 119 clinical samples, both Control-FREEC and CNVkit called 71.8% and 94%, respectively, of the SCNAs found by the SNP arrays, but with a considerable amount of false positives (precision 29% and 4.9%). Whole exome and targeted gene panel methods by design limit the precision of SCNA callers, making them prone to false positives. SCNA calls cannot easily be integrated in clinical pipelines that use data from targeted capturebased sequencing. If used at all, they need to be cross-validated using orthogonal methods.

24. Comprehensive benchmarking of SNV callers for highly admixed tumors.

Precision medicine attempts to individualize cancer therapy by matching tumor-specific genetic changes with effective targeted therapies. A crucial first step in this process is the reliable identification of cancer-relevant variants, which is considerably complicated by the impurity and heterogeneity of clinical tumor samples. We compared the impact of admixture of non-cancerous cells and low somatic allele frequencies on the sensitivity and precision of 19 state-of-the-art SNV callers. We studied both whole exome and targeted gene panel data and up to 13 distinct parameter configurations for each tool. We found vast differences among callers.

Based on our comprehensive analyses we recommend joint tumor-normal calling with MuTect, EBCall or Strelka for whole exome somatic variant calling, and HaplotypeCaller or FreeBayes for whole exome germline calling. For targeted gene panel data on a single tumor sample, LoFreqStar performed best. We further found that tumor impurity and admixture had a negative impact on precision, and in particular, sensitivity in whole exome experiments. At admixture levels of 60% to 90% sometimes seen in pathological biopsies, sensitivity dropped significantly, even when variants were originally present in the tumor at 100% allele frequency. Sensitivity to low-frequency SNVs improved with targeted panel data, but whole exome data allowed more efficient identification of germline variants. Effective somatic variant calling requires high-quality pathological samples with minimal admixture, a consciously selected sequencing strategy, and the appropriate variant calling tool with settings optimized for the chosen type of data.

25. Bioinformatory-assisted analysis of next-generation sequencing data for precision medicine in pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) is a tumor with an extremely poor prognosis, predominantly as a result of chemotherapy resistance and numerous somatic mutations. Consequently, PDAC is a prime candidate for the use of sequencing to identify causative mutations, facilitating subsequent administration of targeted therapy. In a feasibility study,
we retrospectively assessed the therapeutic recommendations of a novel, evidence-based software that analyzes next-generation sequencing (NGS) data using a large panel of pharmacogenomic biomarkers for efficacy and toxicity. Tissue from 14 patients with PDAC was sequenced using NGS with a 620 gene panel. FASTQ files were fed into treatmentmap.

The results were compared with chemotherapy in the patients, including all side effects. No changes in therapy were made. Known driver mutations for PDAC were confirmed (e.g. KRAS, TP53). Software analysis revealed positive biomarkers for predicted effective and ineffective treatments in all patients. At least one biomarker associated with increased toxicity could be detected in all patients. Patients had been receiving one of the currently approved chemotherapy agents. In two patients, toxicity could have been correctly predicted by the software analysis. The results suggest that NGS, in combination with an evidence-based software, could be conducted within a 2-week period, thus being feasible for clinical routine. Therapy recommendations were principally off-label use.

Based on the predominant KRAS mutations, other drugs were predicted to be ineffective. The pharmacogenomic biomarkers indicative of increased toxicity could be retrospectively linked to reported negative side effects in the respective patients. Finally, the occurrence of somatic and germline mutations in cancer syndrome-associated genes is noteworthy, despite a high frequency of these particular variants in the background population. These results suggest software-analysis of NGS data provides evidence-based information on effective, ineffective and toxic drugs, potentially forming the basis for precision cancer medicine in PDAC.

26. Association between serotonin syndrome and second-generation antipsychotics via pharmacological target-adverse event analysis.

Case reports suggest an association between second-generation anti-psychotics (SGAs) and serotonin syndrome (SS). The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) was analyzed to generate hypotheses about how SGAs may interact with pharmacological targets associated with SS. FAERS was integrated with additional sources to link information about adverse events with drugs and targets.

Using Proportional Reporting Ratios, we identified signals that were further investigated with the literature to evaluate mechanistic hypotheses formed from the integrated FAERS data. Analysis revealed common pharmacological targets perturbed in both SGA and SS cases, indicating that SGAs may induce SS. The literature also supported 5-HT2A antagonism and 5-HT1A agonism as common mechanisms that may explain the SGA-SS association. Additionally, integrated FAERS data mining and case studies suggest that interactions between SGAs and other serotonergic agents may increase the risk for SS. Computational analysis can provide additional insights into the mechanisms underlying the relationship between SGAs and SS.
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27. In silico profiling of clinical phenotypes for human targets using adverse event data.

We present a novel approach for the molecular transformation and analysis of patient clinical phenotypes. Building on the fact that drugs perturb the function of targets/genes, we integrated data from 8.2 million clinical reports detailing drug-induced side effects with the molecular world of drug-target information. Using this dataset, we extracted 1.8 million associations of clinical phenotypes to 770 human drug-targets. This collection is perhaps the largest phenotypic profiling reference of human targets to-date, and unique in that it enables rapid development of testable molecular hypotheses directly from humanspecific information.

We also present validation results demonstrating analytical utilities of the approach, including drug safety prediction, and the design of novel combination therapies. Challenging the long-standing notion that molecular perturbation studies cannot be performed in humans, our data allows researchers to capitalize on the vast tomes of clinical information available throughout the healthcare system.

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28. A neural autoencoder approach for document ranking and query refinement in pharmacogenomic information retrieval.

In this study, we investigate learning-to-rank and query refinement approaches for information retrieval in the pharmacogenomic domain. The goal is to improve the information retrieval process of biomedical curators, who manually build knowledge bases for personalized medicine.

We study how to exploit the relationships between genes, variants, drugs, diseases and outcomes as features for document ranking and query refinement. For a supervised approach, we are faced with a small amount of annotated data and a large amount of unannotated data. Therefore, we explore ways to use a neural document auto-encoder in a semi-supervised approach. We show that a combination of established algorithms, featureengineering and a neural auto-encoder model yield promising results in this setting.

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29. Target-adverse event profiles to augment pharmacovigilance: A pilot study with six new molecular entities.

Clinical trials can fail to detect rare adverse events (AEs). We assessed the ability of pharmacological target adverse-event (TAE) profiles to predict AEs on US Food and Drug Administration (FDA) drug labels at least 4 years after approval. TAE profiles were generated by aggregating AEs from the FDA adverse event reporting system (FAERS) reports and the FDA drug labels for drugs that hit a common target. A genetic algorithm (GA) was used to choose the adverse event (AE) case count (N), disproportionality score in FAERS (proportional reporting ratio (PRR)), and percent of comparator drug labels with an AE to maximize F-measure.

With FAERS data alone, precision, recall, and specificity were 0.57, 0.78, and 0.61, respectively. After including FDA drug label data, precision, recall, and specificity improved to 0.67, 0.81, and 0.71, respectively. Eighteen of 23 (78%) postmarket label changes were identified correctly. TAE analysis shows promise as a method to predict AEs at the time of drug approval.

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US Food & Drug Administration, Center for Drug Evaluation and Research. USA

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30. Adverse event circumstances and the case of drug interactions.

Adverse events are a common and for the most part unavoidable consequence of therapeutic intervention. Nevertheless, available tomes of such data now provide us with an invaluable opportunity to study the relationship between human phenotype and druginduced protein perturbations within a patient system. Deciphering the molecular basis of such adverse responses is not only paramount to the development of safer drugs but also presents a unique opportunity to dissect disease systems in search of novel response biomarkers, drug targets, and efficacious combination therapies.

Inspired by the potential applications of this approach, we first examined adverse event circumstances reported in FAERS and then performed a molecular level interrogation of cancer patient adverse events to investigate the prevalence of drug-drug interactions in the context of patient responses. We discuss avoidable and/or preventable cases and how molecular analytics can help optimize therapeutic use of co-medications. While up to one out of three adverse events in this dataset might be explicable by iatrogenic, patient, and product/device related factors, almost half of the patients in FAERS received multiple drugs and one in four may have experienced effects attributable to drug interactions.

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31. Precision Oncology - The quest for evidence.

The molecular characterization of patient tumors provides a rational and highly promising approach for guiding oncologists in treatment decision-making. Notwithstanding, genomic medicine still remains in its infancy, with innovators and early adopters continuing to carry a significant portion of the clinical and financial risk. Numerous innovative precision oncology trials have emerged globally to address the associated need for evidence of clinical utility.

These studies seek to capitalize on the power of predictive biomarkers and/or treatment decision support analytics, to expeditiously and cost-effectively demonstrate the positive impact of these technologies on drug resistance/response, patient survival, and/or quality of life. Here, we discuss the molecular foundations of these approaches and highlight the diversity of innovative trial strategies that are capitalizing on this emergent knowledge. We conclude that, as increasing volumes of clinico-molecular outcomes data become available, in future, we will begin to transition away from expert systems for treatment decision support (TDS), towards the power of AI-assisted TDS-an evolution that may truly revolutionize the nature and success of cancer patient care.

Journal

Journal of
Personalized Medicine

Reference

J Pers Med. 2019 Sep 5;9(3). pii:E43.n
PMID: 31492009

2019

Collaborator

MOLECULAR
HEALTH

Technology

GUIDE

32. Radioimmunotherapy in non-Hodgkin's Lymphoma: Retrospective adverse event profiling of zevalin and bexxar.

The development of monoclonal antibodies has dramatically changed the outcome of patients with non-Hodgkin's lymphoma (NHL), the most common hematological malignancy. However, despite the satisfying results of monoclonal antibody treatment, only few NHL patients are permanently cured with single-agent therapies. In this context, radioimmunotherapy, the administration of radionuclides conjugated to monoclonal antibodies, is aimed to augment the single-agent efficacy of immunotherapy in order to deliver targeted radiation to tumors, particularly CD20+ B-cell lymphomas.

Based on evidence from several trials in NHL, the radiolabeled antibodies 90Y-ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals) and 131I-tositumomab (Bexxar, GlaxoSmithKline) received FDA approval in 2002 and 2003, respectively. However, none of the two radioimmunotherapeutic agents has been broadly applied in clinical practice. The main reason for the under-utilization of radioimmunotherapy includes economic and logistic considerations. However, concerns about potential side effects have also been raised. Driven by these developments, we performed retrospective analysis of adverse events reporting Zevalin or Bexxar, extracted from the FDA's Adverse Event Reporting System (FAERS) and the World Health Organization's VigiBase repository.

Our results indicate that the two radioimmunotherapeutic agents have both related and distinct side effect profiles and confirm their known toxicological considerations. Our work also suggests that computational analysis of real-world post-marketing data can provide informative clinical insights. While more prospective studies are necessary to fully characterize the efficacy and safety of radioimmunotherapy, we expect that it has not yet reached its full therapeutic potential in modern hematological oncology.

Journal

pharmaceuticals

Reference

Pharmaceuticals 2019, 12(4), 141.
doi: 10.3390/ph12040141.

2019

Collaborator

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33. Consolidated BRCA1/2 Variant Interpretation by MH BRCA Correlates with Predicted PARP Inhibitor Efficacy Association by MH Guide.

BRCA1/2 variants are prognostic biomarkers for hereditary breast and/or ovarian cancer (HBOC) syndrome and predictive biomarkers for PARP inhibition. In this study, we benchmarked the classification of BRCA1/2 variants from patients with HBOC-related cancer using MH BRCA, a novel computational technology that combines the ACMG guidelines with expert-curated variant annotations. Evaluation of BRCA1/2 variants (n = 1040) taken from four HBOC studies showed strong concordance within the pathogenic (98.1%) subset. Comparison of MH BRCA's ACMG classification to ClinVar submitter content from ENIGMA, the international consortium of investigators on the clinical significance of BRCA1/2 variants, the ARUP laboratories, a clinical testing lab of the University of UTAH, and the German Cancer Consortium showed 99.98% concordance (4975 out of 4976 variants) in the pathogenic subset.

In our patient cohort, refinement of patients with variants of unknown significance reduced the uncertainty of cancer-predisposing syndromes by 64.7% and identified three cases with potential family risk to HBOC due to a likely pathogenic variant BRCA1 p.V1653L (NM_007294.3:c.4957G > T; rs80357261). To assess whether classification results predict PARP inhibitor efficacy, contextualization with functional impact information on DNA repair activity were performed, using MH Guide. We found a strong correlation between treatment efficacy association and MH BRCA classifications. Importantly, low efficacy to PARP inhibition was predicted in 3.95% of pathogenic variants from four examined HBOC studies and our patient cohort, indicating the clinical relevance of the consolidated variant interpretation.

Journal

International Journal of Molecular Sciences

Reference

Int J Mol Sci. 2020; 21(11):3895.
PMID:32486089

2020

Collaborator

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地方独立行政法人山梨県立病院機構
山梨県立中央病院
YAMANASHI PREFECTURAL CENTRAL HOSPITAL

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GUIDE/BRCA

34. Public Adverse Event Data Insights into the Safety of Pembrolizumab in Melanoma Patients.

Immune checkpoint inhibition represents an important therapeutic option for advanced melanoma patients. Results from clinical studies have shown that treatment with the PD-1 inhibitors Pembrolizumab and Nivolumab provides improved response and survival rates. Moreover, combining Nivolumab with the CTLA-4 inhibitor Ipilimumab is superior to the respective monotherapies. However, use of these immunotherapies is frequently associated with, sometimes life-threatening, immune-related adverse events. Thus, more evidence-based studies are required to characterize the underlying mechanisms, towards more effective clinical management and treatment monitoring. Our study examines two sets of public adverse event data coming from FAERS and VigiBase, each with more than two thousand melanoma patients treated with Pembrolizumab.

Standard disproportionality metrics are utilized to characterize the safety of Pembrolizumab and its reaction profile is compared to those of the widely used Ipilimumab and Nivolumab based on melanoma cases that report only one of them. Our results confirm known toxicological considerations for their related and distinct side-effect profiles and highlight specific immune-related adverse reactions. Our retrospective computational analysis includes more patients than examined in other studies and relies on evidence coming from public pharmacovigilance data that contain safety reports from clinical and controlled studies as well as reports of suspected adverse events coming from real-world post-marketing setting. Despite these informative insights, more prospective studies are necessary to fully characterize the efficacy of these agents.

Journal
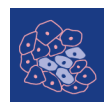
cancers

Reference

Cancers (Basel). 2020;12(4):1008.
https://www.mdpi.com/2072-6694/12/4/1008

2020

Collaborator

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Technology

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35. Target Adverse Event Profiles for Predictive Safety in the Postmarket Setting.

We improved a previous pharmacological target adverse-event (TAE) profile model to predict adverse events (AEs) on US Food and Drug Administration (FDA) drug labels at the time of approval. The new model uses more drugs and features for learning as well as a new algorithm. Comparator drugs sharing similar target activities to a drug of interest were evaluated by aggregating AEs from the FDA Adverse Event Reporting System (FAERS), FDA drug labels, and medical literature. An ensemble machine learning model was used to evaluate FAERS case count, disproportionality scores, percent of comparator drug labels with a specific AE, and percent of comparator drugs with the reports of the event in the literature. Overall classifier performance was F1 of 0.71, area under the precision-recall curve of 0.78, and area under the receiver operating characteristic curve of 0.87. TAE analysis continues to show promise as a method to predict adverse events at the time of approval.

Journal

Clinical Pharmacology & Therapeutics

Reference

Clin Pharm & Therap Vol 109, Issue 5, 1232-1243. doi:10.1002/cpt.2074

2021

Collaborator

FDA — US Food & Drug Administration, Center for Drug Evaluation and Research. USA

Technology

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36. A case study of a patient-centered reverse translational systems-based approach to understand adverse event profiles in drug development.

Adverse drug reactions (ADRs) of targeted therapy drugs (TTDs) are frequently unexpected and long-term toxicities detract from exceptional efficacy of new TTDs. In this proof-of-concept study, we explored how molecular causation involved in trastuzumab-induced cardiotoxicity changes when trastuzumab was given in combination with doxorubicin, tamoxifen, paroxetine, or lapatinib. The data analytical platform Molecular Health Effect was utilized to map population ADR data from the US Food and Drug Administration (FDA) Adverse Event Reporting System to chemical and biological databases (such as UniProt and Reactome), for hypothesis generation regarding the underlying molecular mechanisms causing cardiotoxicity. Disproportionality analysis was used to assess the statistical relevance between adverse events of interest and molecular causation. Literature search was performed to compare the established hypotheses to published experimental findings.

We found that the combination therapy of trastuzumab and doxorubicin may affect mitochondrial dysfunction in cardiomyocytes through different molecular pathways such as BCL-X and PGC-1α proteins, leading to a synergistic effect of cardiotoxicity. We found, on the other hand, that trastuzumab-induced cardiotoxicity would be diminished by concomitant use of tamoxifen, paroxetine, and/or lapatinib. Tamoxifen and paroxetine may cause less cardiotoxicity through an increase in antioxidant activities, such as glutathione conjugation. Lapatinib may decrease the apoptotic effects in cardiomyocytes by altering the effects of trastuzumab on BCL-X proteins. This patient-centered systems-based approach provides, based on the trastuzumab-induced ADR cardiotoxicity, an example of how to apply reverse translation to investigate ADRs at the molecular pathway and target level to understand the causality and prevalence during drug development of novel therapeutics.

Journal

CTS Clinical and Translational Science
An Official Journal of ASCPT
Open Access

Reference

Kim, S. et al. Clin Transl Sci . 2022;15(4):1003-1013. doi: 10.1111/cts.13219

2021

Collaborator

UF UNIVERSITY of FLORIDA   thinkQ²

Takeda

Technology

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37. Application of a patient-centered reverse translational systems-based approach to understand mechanisms of an adverse drug reaction of immune checkpoint inhibitors.

Immunotherapy became a key pillar of cancer therapeutics with the approvals of ipilimumab, nivolumab, and pembrolizumab, which inhibit either cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed death-1 (PD-1) that are negative regulators of T-cell activation. However, boosting T-cell activation is often accompanied by autoimmunity, leading to adverse drug reactions (ADRs), including high grade 3-4 colitis and its severe complications whose prevalence may reach 14% for combination checkpoint inhibitors. In this research, we investigated how mechanistic differences between anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab and pembrolizumab) affect colitis, a general class toxicity.

The data analytical platform Molecular Health Effect was utilized to map population ADR data from the US Food and Drug Administration (FDA) Adverse Event Reporting System to chemical and biological databases for hypothesis generation regarding the underlying molecular mechanisms causing colitis. Disproportionality analysis was used to assess the statistical relevance between adverse events of interest and molecular causation. We verified that the anti-CTLA-4 drug is associated with an approximately three-fold higher proportional reporting ratio associated with colitis than those of the anti-PD-1 drugs.

The signal of the molecular mechanisms, including signaling pathways of inflammatory cytokines, was statistically insignificant to test the hypothesis that the severer rate of colitis associated with ipilimumab would be due to a greater magnitude of T-cell activation as a result of earlier response of the anti-CTLA-4 drug in the immune response. This patient-centered systems-based approach provides an exploratory process to better understand drug pair adverse events at pathway and target levels through reverse translation from postmarket surveillance safety reports.

Journal

Reference

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Technology

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38. Advancing drug safety science by integrating molecular knowledge with post-marketing adverse event reports.

Promising drug development efforts may frequently fail due to unintended adverse reactions. Several methods have been developed to analyze such data, aiming to improve pharmacovigilance and drug safety. In this work, we provide a brief review of key directions to quantitatively analyzing adverse events and explore the potential of augmenting these methods using additional molecular data descriptors. We argue that molecular expansion of adverse event data may provide a path to improving the insights gained through more traditional pharmacovigilance approaches.

Examples include the ability to assess statistical relevance with respect to underlying biomolecular mechanisms, the ability to generate plausible causative hypotheses and/or confirmation where possible, the ability to computationally study potential clinical trial designs and/or results, as well as the further provision of advanced features incorporated in innovative methods, such as machine learning. In summary, molecular data expansion provides an elegant way to extend mechanistic modeling, systems pharmacology, and patient-centered approaches for the assessment of drug safety.

We anticipate that such advances in real-world data informatics and outcome analytics will help to better inform public health, via the improved ability to prospectively understand and predict various types of drug-induced molecular perturbations and adverse events.

Journal

Reference

Collaborator

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Technology

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39. Evaluation of the TruSight Tumor 170 Assay and Its Value in Clinical Diagnostics.

Background: Parallel sequencing technologies have become integrated into clinical practice. This study evaluated the TruSight Tumor 170 assay for the simultaneous detection of somatic gene mutations (SNPs and indels), gene fusions and CNVs, and its implementation into routine diagnostics. Methods: Forty-four formalin-fixed, paraffin-embedded tissue samples analyzed previously with validated methods were evaluated with the TruSight Tumor 170 assay (Illumina). For data analysis the TruSight Tumor 170 app, the BaseSpace Variant Interpreter (Illumina), and the Molecular Health Guide Software (Molecular Health) were used. Results: All somatic gene mutations were identified when covered by the assay.

Two high-level MET amplifications were detected by CNV analysis.
Focal MET amplifications with a copy number below 10 were not reliably detected at the DNA-level. Twenty-one of 31 fusions and splice variants were confirmed with the assay on the RNA-level. The remaining eight aberrations were incorrect by previous methods. In two cases, no splicing was observed. Conclusions: The TruSight Tumor 170 gives reliable results even if low DNA and RNA concentrations are applied in comparison to other methods and can be used in a routine workflow to detect somatic gene mutations, gene fusions, and splice variants. However, we were not able to detect most focal gene amplifications/deletions.

Journal

Journal of *Molecular Pathology*

Reference

J. Mol. Pathol. 2022, 3(1), 53-67.
https://doi.org/10.3390/jmp3010006

2022

Collaborator

UNIKLINIK KÖLN

Technology

GUIDE

40. The COVID-19 Explorer – an integrated, whole patient knowledge model of COVID-19 disease.

Since early 2020 the COVID-19 pandemic has paralyzed the world, resulting in more than half a billion infections and over 6 million deaths within a 28-month period. Knowledge about the disease remains largely disjointed, especially when considering the molecular mechanisms driving the diversity of clinical manifestations and symptoms. Despite the recent availability of vaccines, there remains an urgent need to develop effective treatments for cases of severe disease, especially in the face of novel virus variants.

The complexity of the situation is exacerbated by the emergence of COVID-19 as a complex and multifaceted systemic disease affecting independent tissues and organs throughout the body. The development of effective treatment strategies is therefore predicated on an integrated understanding of the underlying disease mechanisms and their potentially causative link to the diversity of observed clinical phenotypes. To address this need, we utilized a computational technology (the Dataome platform) to build an integrated clinico-molecular view on the most important COVID-19 clinical phenotypes. Our results provide the first integrated, whole-patient model of COVID-19 symptomatology that connects the molecular lifecycle of SARS-CoV-2 with microvesicle-mediated intercellular communication and the contact activation and kallikrein-kinin systems.

The model not only explains the clinical pleiotropy of COVID-19, but also provides an evidence-driven framework for drug development/repurposing and the identification of critical risk factors. The associated knowledge is provided in the form of the open source COVID-19 Explorer (https://covid19.molecularhealth.com), enabling the global community to explore and analyze the key molecular features of systemic COVID-19 and associated implications for research priorities and therapeutic strategies. Our work suggests that knowledge modeling solutions may offer important utility in expediting the global response to future health emergencies.

Journal

frontiers

Reference

Front. Mol. Med. 2022, 2:1035215
doi: 10.3389/fmmed.2022.1035215

2022

Collaborator

ETH zürich

University of Zurich UZH

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UNIVERSITÄTSMEDIZIN BERLIN

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41. Whole patient knowledge modeling of COVID-19 symptomatology reveals common molecular mechanisms.

Infection with SARS-CoV-2 coronavirus causes systemic, multi-faceted COVID-19 disease. However, knowledge connecting its intricate clinical manifestations with molecular mechanisms remains fragmented. Deciphering the molecular basis of COVID-19 at the whole-patient level is paramount to the development of effective therapeutic approaches.

With this goal in mind, we followed an iterative, expert-driven process to compile data published prior to and during the early stages of the pandemic into a comprehensive COVID-19 knowledge model. Recent updates to this model have also validated multiple earlier predictions, suggesting the importance of such knowledge frameworks in hypothesis generation and testing. Overall, our findings suggest that SARS-CoV-2 perturbs several specific mechanisms, unleashing a pathogenesis spectrum, ranging from "a perfect storm" triggered by acute hyper-inflammation, to accelerated aging in protracted "long COVID-19" syndromes. In this work, we shortly report on these findings that we share with the community via 1) a synopsis of key evidence associating COVID-19 symptoms and plausible mechanisms, with details presented within 2) the accompanying "COVID-19 Explorer" webserver, developed specifically for this purpose (found at https://covid19.molecularhealth.com).

We anticipate that our model will continue to facilitate clinico-molecular insights across organ systems together with hypothesis generation for the testing of potential repurposing drug candidates, new pharmacological targets and clinically relevant biomarkers. Our work suggests that whole patient knowledge models of human disease can potentially expedite the development of new therapeutic strategies and support evidence-driven clinical hypothesis generation and decision making.

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42. Upregulation of miRNA-200c during disease progression in COVID-19 patients.

The COVID-19 pandemic has caused more than 6 million deaths worldwide since its first outbreak in December 2019 and continues to be a major health problem. Several studies have established that the infection by SARS-CoV-2 can be categorized in a viremic, acute and recovery or severe phase. Hyperinflammation during the acute pneumonia phase is a major cause of severe disease progression and death. Treatment of COVID-19 with directly acting antivirals is limited within a narrow window of time between first clinical symptoms and the hyperinflammatory response. Therefore, early initiation of treatment is crucial to assure optimal health care for patients. Molecular diagnostic biomarkers represent a potent tool to predict the course of disease and thus to assess the optimal treatment regimen and time point. Here, we investigated miRNA-200c as a potential marker for the prediction of the severity of COVID-19 to preventively initiate and personalize therapeutic interventions in the future. We found that miRNA-200c correlates with the severity of disease. With retrospective analysis, however, there is no correlation with prognosis at the time of hospitalization. Our study provides the basis for further evaluation of miRNA-200c as a predictive biomarker for the progress of COVID-19.

Collaborator

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43. Determination of The Cancer Genome Atlas (TCGA) Endome-trial Cancer Molecular Subtypes Using the Variant Interpretation and Clinical Decision Support Software MH Guide.

Background: The Cancer Genome Atlas (TCGA) network (United States National Cancer Institute) identified four molecular endometrial cancer (EC) subtypes using an extensive multi-method approach. The aim of this study was to determine the four TCGA EC molecular subtypes using a single-method whole-exome sequencing (WES)-based approach provided by MH Guide (Molecular Health, Heidelberg, Germany). Methods: WES and clinical data of n = 232 EC patients were obtained from TCGA. The four TCGA EC molecular subtypes designated as (i) Mutated Polymerase ε (POLE), (ii) Microsatellite Instability (MSI), (iii) Copy Number (CN) low and, (iv) CN-high were determined using the MH Guide software. The prognostic value of the subtypes determined by MH Guide were compared with the TCGA classification. Results: Analysis of WES data using the MH Guide software led to the precise identification of the four EC molecular subtypes analogous to the TCGA classification. Both approaches displayed high concordance in terms of prognostic significance. Conclusions: The multi-method-based TCGA EC molecular subtypes can reliably be reproduced by the single-method-based MH Guide approach. The easy-to-implement single-method MH Guide approach represents a promising diagnostic tool.

Journal
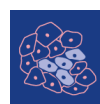
cancers

Reference

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2023

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44. Rewiring Drug Research and Development through Human Data-Driven Discovery (HD3).

In an era of unparalleled technical advancement, the pharmaceutical industry is struggling to transform data into increased research and development efficiency, and, as a corollary, new drugs for patients. Here, we briefly review some of the commonly discussed issues around this counterintuitive innovation crisis. Looking at both industry- and science-related factors, we posit that traditional preclinical research is front-loading the development pipeline with data and drug candidates that are unlikely to succeed in patients. Applying a first principles analysis, we highlight the critical culprits and provide suggestions as to how these issues can be rectified through the pursuit of a Human Data-driven Discovery (HD3) paradigm. Consistent with other examples of disruptive innovation, we propose that new levels of success are not dependent on new inventions, but rather on the strategic integration of existing data and technology assets. In support of these suggestions, we highlight the power of HD3, through recently published proof-of-concept applications in the areas of drug safety analysis and prediction, drug repositioning, the rational design of combination therapies and the global response to the COVID-19 pandemic. We conclude that innovators must play a key role in expediting the path to a largely human-focused, systems-based approach to drug discovery and research.

Journal

pharmaceutics

Reference

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Collaborator

FDA — US Food & Drug Administration, Center for Drug Evaluation and Research. USA

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45. Whole Exome Analysis to Select Targeted Therapies for Patients with Metastatic Breast Cancer – A Feasibility Study.

Introduction: The purpose of this feasibility study was to select targeted therapies according to "ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)". Data interpretation was further supported by a browser-based Treatment Decision Support platform (MH Guide, Molecular Health, Heidelberg, Germany).

Patients: We applied next generation sequencing based whole exome sequencing of tumor tissue and peripheral blood of patients with metastatic breast cancer (n = 44) to detect somatic as well as germline mutations.

Results: In 32 metastatic breast cancer patients, data interpretation was feasible. We identified 25 genomic alterations with ESCAT Level of Evidence I or II in 18/32 metastatic breast cancer patients, which were available for evaluation: three copy number gains in *HER2* , two g *BRCA1* , two g *BRCA2* , six *PIK3CA,* one *ESR1* , three *PTEN* , one *AKT1* and two *HER2* mutations. In addition, five samples displayed Microsatellite instability high-H.

Conclusions: Resulting treatment options were discussed in a tumor board and could be recommended in a small but relevant proportion of patients with metastatic breast cancer (7/18). Thus, this study is a valuable preliminary work for the establishment of a molecular tumor board within the German initiative "Center for Personalized Medicine" which aims to shorten time for analyses and optimize selection of targeted therapies.

Journal

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46. Determination of endometrial cancer molecular subtypes using a whole exome-sequencing based single-method approach.

Aim

Endometrial cancer (EC) is heterogeneous with respect to epidemiology, clinical course, histopathology and tumor biology. Recently, The Cancer Genome Atlas (TCGA) network has identified four molecular subtypes with distinct clinical courses by an integrated multi-omics approach. These subtypes are of critical importance in the clinical management of EC. However, determination of TCGA molecular subtypes requires a complex methodological approach that is resource intensive and difficult to implement in diagnostic routine procedures. In this context, Talhouk et al. reported the precise determination of modified subtypes based on molecular surrogates obtained by a two-method approach comprising immunohistochemistry and DNA-sequence analysis (Proactive Molecular Risk Classifier for Endometrial Cancer; ProMisE). In this study, we aimed to identify EC molecular subtypes in analogy to TCGA and ProMisE applying an innovative whole exome-sequencing (WES) based single-method approach.

Methods

WES was performed in a cohort comprising N = 114 EC patients. WES data were analyzed using the oncology treatment decision support software MH Guide (Molecular Health, Heidelberg, Germany) and EC molecular subtypes in analogy to TCGA and ProMisE were determined. Results from both classifications were compared regarding their prognostic values using overall survival and progression-free survival analyses.

Results

Applying a single-method WES-approach, EC molecular subtypes analogue to TCGA and ProMisE were identified in the study cohort. The surrogate marker-analogue classification precisely identified high-risk and low-risk EC, whereas the TCGA-analogue classification failed to obtain significant prognostic values in this regard.

Conclusions: Our data demonstrate that determination of EC molecular subtypes analogue to TCGA and ProMisE is feasible by using a single-method WES approach. Within our EC cohort, prognostic implications were only reliably provided by applying the surrogate marker-analogue approach. Designation of molecular subtypes in EC will be increasingly important in routine clinical practice. Thus, the single-method WES approach provides an important simple tool to tailor therapeutic decisions in EC.

Journal

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47. Histopathologic, Molecular, and Clinical Profiling of Lymphoepithelioma-like Carcinoma of the Bladder.

Lymphoepithelioma-like carcinoma of the bladder (LELC-B) is a rare histologic subtype characterized by strong immune cell (IC) infiltrates. A better prognosis and favorable response rates to immune checkpoint inhibitors have been described. We aimed to characterize the molecular profiles and IC infiltration of LELC-B for a better understanding of its therapeutic implications. We identified 11 muscle-invasive bladder cancer cases with pure and mixed LELC-B. Programmed cell death ligand-1 (PD-L1) expression and mismatch repair proteins were evaluated using immunohistochemistry. We calculated the tumor mutational burden and characterized mutational profiles using whole-exome DNA sequencing data. Transcriptomic signatures were detected using the NanoString nCounter PanCancer IO360 Panel. Multiplex immunofluorescence of tumor microenvironment (PD-L1, PanCK, α-SMA, vimentin, CD45, and Ki67) and T cells (CD4, CD3, PD-1, CD163, CD8, and FoxP3) was used to quantify cell populations. All LELC-B cases were highly positive for PD-L1 (median tumor proportion score/tumor cell, 70%; range, 20%-100%; median combined positive score, 100; range, 50-100) and mismatch repair proficient and negative for Epstein-Barr virus infection. IC infiltrates were characterized by a high CD8+ T-cell count and high PD-1/PD-L1 expression on immune and tumor cells. LELC-B showed upregulation of signaling pathways involved in IC response. Most common mutations were found in chromatin remodeling genes causing epigenetic dysregulation. All LELC-B cases showed high tumor mutational burden with a median of 39 mutations/Mb (IQR, 29-66 mutations/Mb). In conclusion, LELC-B is a highly immunogenic tumor, showing strong upregulation of PD-1/PD-L1 and making immune checkpoint inhibitors a promising treatment option.

48. Molecular tumor board for gynecologic malignancies: the real-world experience from the Department for Gynecology and Gynecologic Oncology of Kliniken Essen-Mitte

Objective
Advances in cancer research are leading to a shift from the traditional "organ-centric" therapies to a personalized tumor biology-based approach. Here, we report outcomes in patients who underwent molecular tumor profiling for gynecologic malignancies.

Methods
We prospectively recorded clinical and pathologic characteristics, follow-up data, next-generation sequencing results, and tumor board recommendations of all patients who underwent molecular tumor board at the Department for Gynecologic Oncology, Kliniken Essen-Mitte, from March 2019 to March 2024. Progression-free survival ratio was calculated to evaluate the benefit of the molecular tumor board-recommended treatment (progression-free survival after molecular tumor board/progression-free survival on previously received treatment).

Results
Altogether, 237 patients with the median number of previous lines of 3 were discussed at the molecular tumor board. High-grade serous ovarian cancer was the most common diagnosis (n = 148, 62.4%). In 220 patients (93%), genomic tumor alterations were found and classified according to the European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets: tier-X (lack of evidence for actionability) n = 94, tier-I (ready for routine use) n = 36, tier-II (investigational) n = 32, tier-IV (hypothetical target) n = 37, and tier-V (combination development) n = 6. The most common alterations were found in TP53 (n = 142), BRCA1 (n = 22), KRAS (n = 16), PIK3CA (n = 15), FOXL2 (n = 15), GSTP1 (n = 11), PTEN (n = 8), CDKN2A/B (n = 7), and others (n = 126). The next-generation sequencing results affected the molecular tumor board decision in 65 patients (27.4%), with 9 patients (3.8%) receiving a biomarker-based therapy; 8 patients (88.9%) experienced disease control lasting over 3 months, and 6 of these (66.7%) showed a progression-free survival ratio ≥1.3. The most common causes of not following the molecular tumor board decision were best supportive care or death (n = 21), no progression (n = 14), or starting another treatment (n = 6).

Conclusions
Molecular tumor profiling provided additional treatment strategies in a meaningful number of patients. Earlier inclusion in the molecular tumor board might lead to increased applicability of results for patients.

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