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Commentary

Bringing Cancer Biomarkers to Clinical Fruitions

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Abstract

In the cancer biomarker field, despite the numerous investments and extensive efforts during the past decades, only less than 24 have been approved by the FDA and far fewer are currently using in clinics for cancer detection and diagnosis. This commentary intended to present the author's personal point of view on the possible reasons for the slow progress, and also offers the potential solutions to improve the biomarker development processes. In addition, this commentary intended to re-introduce the Early Detection Research Network (EDRN), which was formed by the National Cancer Institute (NCI) in year 2000 to facilitate the discovery, development, and validation of biomarkers for early cancer detection and risk assessment.

Commentary

In the field of biomarkers, much of the biomarker research remains "stuck" at the discovery phase. Some investigators reiterate the discovery process but do not proceed beyond that point. They do not seem committed to moving their findings beyond the early discovery phase. Issues of credit, publication priority, and patent credit have slowed progress into validation.

To date, less than 24 cancer biomarkers have been approved by the FDA and only a few are for cancer detection and diagnosis. Biomarker research requires a knowledge-driven

述评

让肿瘤生物标记物在临床开花结果

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摘要

在癌症生物标记物领域，尽管在过去几十年中的众多投资和辛勤努力，仅有不足 24 个生物标记获食品和药物管理局批准。目前在临床上用于癌症检测与诊断的生物标记则更少。本评论旨在介绍作者本人关于为何生物标记研发如此缓慢的可能原因以及改善此过程的可行方法。除此，作者重温美国家癌症研究所 （NCI）在 2000 年设立的早期检测研究网络（EDRN）。 此网络旨在促进发现，开发， 与验证可用于癌症早期检测和风险评估的生物标记。

述评

在生物标志物领域中，很多生物标志物的研究仍然是"卡"在发现阶段。一些研究人员只是热衷于重复发现的过程，乐意原地踏步。他(她)们似乎缺乏超越早期发现阶段的意志和信心。同时，沽名钓誉，追求文章和专利的不正之风也极大的阻碍了生物标记物的验证过程。

到目前为止，少于 24 种生物标记物已被 FDA 批准；其中，仅有少数几个已用于临床肿瘤检测和诊断。 生物标志物研究需要一个知识驱

environment, in which investigators generate, contribute, manage and analyze data available from a variety of sources and technology platforms. The goal is a continuous feedback loop to accelerate the translation of data into knowledge.

Collaboration, data sharing, data integration and standards are integral. Only by seamlessly structuring and integrating these data types will the complex and underlying causes and outcomes of illness be revealed and effective prevention, early detection and personalized treatments be realized. Successful translation of biomarkers into clinical application depends on the biomarkers entering into the validation pipeline.

No matter how well thought out and rigorous the translation process, if the biomarkers lack requisite the useful performance characteristics, they will not be successfully translated into clinical application. Unfortunately, most of the biomarkers reported in the literature have insufficient sensitivity and specificity or lack data using appropriate specimens, e.g. late stage cancers or mismatched cases and controls.

Thus, the first step to enchaining the translation of biomarkers is to improve the discovery process. Whenever possible, discovery should be performed using high quality specimens from carefully matched cases and controls that are collected under the same conditions using a standard operating procedure. It has been suggested that discovery should be performed using specimens collected from asymptomatic patients who later go on to develop cancer.

In 2000, national cancer institute's Early Detection Research Network (EDRN) was formed to facilitate the discovery, development, and validation of biomarkers for early cancer detection and risk assessment. The EDRN is a vertically integrated network composed of four main components. The EDRN brings together investigators from discovery laboratories, clinicians and biostatisticians to discuss issues related to clinical needs and study design and to share resources, such as high quality biospecimens that are collected to address a specific clinical question.

The main objectives of EDRN include: (1) To develop and test promising biomarkers and technologies to guide further testing; (2) To evaluate proven and promising biomarkers and technologies for clinical trials as outcome predictors or surrogate endpoints; (3) To analyze biomarkers and their expression patterns for larger validation studies; (4) To collaborate with

动的环境。在此，科研人员产生、提供，管理，和分析来自不同来源和技术平台的资料数据，其目的是维持一个连续不断的反馈循环，以加速将数据转换为知识的步伐。

协作、数据共享、 数据整合、和标准化是缺一不可的链接。只有通过无缝地构建和整合这些数据类型，将复杂和潜在的病情原因和结果揭示出来，才有可能实现个性化的治疗。生物标志物是否可以成功地进入临床应用，取决于是否该标记物能进入验证渠道。

无论设计如何周密，转化步骤如何严紧，如果生物标志 物 缺乏必要的性能特点，他们将不可能成功地转化为临床应用。不幸的是，大部分文献报道的生物标志物缺乏足够的敏感性和特异性，或者用材不当, 如：使用晚期癌症或错误配对的标本， 或者缺乏适当的对照。

故此，促进生物标记临床转 化 的第一步是改善标记发现的程序。只要可能，生物标记物的发现应该取用高质量的标本。这些标本应严格配对，适当对照，并在相同条件下，以标准程序收取。既往实验已提示：应用于生物标记物发现的材料最好取自没有临床症状但随后发现癌症的病人。

2000 年，美国国家癌症研究所建立了早期检测研究网络 （EDRN），旨在促进生物标记物的发现，开发，和验证，并将此用于癌症早期检测和风险预测。EDRN 是一个直线整合的网络。其含四个主要成份。EDRN 把生物标记物研发人员，临床医生，生物统计字家组合在一起，研讨生物标记研发相关的各种内容，如临床需求，实验设计，共享资源(如供某种临床持殊需求的高质量标本)。

EDRN 的主要目标包括: (1) 开发和测试有前途的生物标志物和技术，以指导进一步测试; (2) 评价行之有效和可取的生物标志物和临床试验技术，作为预后或终点观察目标; (3) 分析生物标志物表达模式，以指导更大的验证研

industrial and academic leaders to develop high-throughput and sensitive assays; (5) To conduct early phase epidemiologic a and clinical studies; (6) to promote collaboration and dissemination of information and avoid fragmentation of effort.

The EDRN has established a national infrastructure to support validation of cancer biomarkers. The EDRN has been able to develop and deploy an infrastructure to support data sharing, knowledge management and collaborative research. The informatics activities within EDRN are led by the Informatics Center at NASA Jet Propulsion Laboratory, Fred Hutchinson Cancer Research Center, and the Dartmouth Medical School. The external link of EDRN is http://edrn.nci.nih.gov.

研究; (4) 配合工业界和学术界的领导人，以制定高吞吐量和敏感的检测; (5) 进行早期阶段流行病学和临床研究; (6) 促进协作和信息传播，避免分散力量。

EDRN 已建成全国性的基础设施，以支持验证的肿瘤生物标记物。EDRN 已经能够开发和部署基础结构以支持数据共享、 知识管理和协作研究。EDRN 内的信息学活动，由在美国国家航空航天局喷气推进实验室、 Fred Hutchinson 癌症研究中心和达特茅斯医学院的信息学中心领导。EDRN 外部链接是 http://edrn.nci.nih.gov 。