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Horizon Scanning for Translational Genomic Research Beyond Bench to Bedside

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Abstract

The dizzying pace of genomic discoveries is leading to an increasing number of clinical applications. However, very little translational research is ongoing beyond Bench to Bedside to assess validity, utility, implementation and outcomes of such applications. Here we report cross sectional results of ongoing horizon scanning of translational genomic research conducted between May 16, 2012 and May 15, 2013. Based on a weekly, systematic query of PubMed, we created a curated set of 505 beyond bench-to-bedside research publications, including 312 original research articles, 123 systematic and other reviews, 38 clinical guidelines, policies and recommendations, and 32 papers describing tools, decision support and educational materials. Most papers (62%) addressed a specific genomic test or other health application; almost half of these (n=180) were related to cancer. We estimate that these publications account for 0.5% of reported human genomics and genetics research during the same time. These data provide baseline information to track the evolving knowledge base and gaps in genomic medicine. Continuous horizon scanning is crucial for an evidence-based translation of genomic discoveries into improved health care and disease prevention.

Keywords

genomic medicine; public health; surveillance; translational research

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INTRODUCTION

Genomics and related fields are becoming increasingly relevant in clinical practice for a wide variety of settings, including the deployment of next generation sequencing in specific scenarios.[1,2] However, the "arrival" of genomics to the bedside in its current state represents only the initial part of the translational highway.[3] Genomic research falls on a continuum of 4 translational phases beyond initial discovery (T0): T1, developing candidate health applications; T2, evaluating candidate health applications and developing evidence-based recommendations; T3, integrating evidence-based recommendations into care and prevention; and T4, assessing health outcomes and population impact.[4] Our notion of this translation highway is highly idealized.[3] A more realistic expectation would be that interventions of putative value will enter clinical practice and only over time will enough evidence be accumulated to support evidence-based guidelines.

Research beyond bench to bedside (T2–T4) supports the evaluation of the clinical validity and utility of promising applications, as well as their comparative effectiveness and implementation and outcomes research to achieve population health benefits.[4] The history of medicine teaches us that premature implementation of promising new technologies without meeting an evidentiary threshold can lead to potential harms and increasing healthcare costs.[3] Yet, almost all current published research in human genomics is in the discovery or "bench to bedside" phase. A previous PubMed analysis found that less than 1% of the published literature on human genomics was related to phases T2 or beyond.[4] This trend follows closely the current level of funding in human genomics research by the National Cancer Institute (only 2% of human genomics research funding goes to T2 or beyond).[5]

Since 2012, the Office of Public Health Genomics, in collaboration with the National Cancer Institute, has been regularly tracking the translational genomics research scientific literature to develop a current baseline for the field and identify opportunities, gaps and challenges in genomic medicine. We briefly summarize the one year data herein, and discuss a process for integrated horizon scanning of such research that can inform research, policy and practice.

METHODS

Each week, the Centers for Disease Control and Prevention (CDC)'s Office of Public Health Genomics publishes the free *Genomics and Health Impact Update* newsletter online and delivers it by e-mail to more than 50,000 subscribers worldwide.[6] Horizon scanning for translational research in this weekly update includes a PubMed targeted search query, supplemented by monitoring of online news using Google Alerts, and genomics-related websites. Publications collected by this process are reviewed and classified by two or more coders according to the schema in Table 1. In this brief report, we limit our analysis and presentation only to papers identified in PubMed beyond bench-to-bedside phases (T2–T4). Because of small numbers, we group products in two groups (T2: what works?) and (T3–T4: how has it been implemented and is it working in the real world?).

RESULTS

During the one-year period from May 16, 2012, through May 15, 2013, 505 articles were identified in PubMed. Of these, 44% were classified as T2 research and 56% as T3 or T4 (Table 2). There were 312 original research articles, 123 reviews, 38 papers describing clinical guidelines, policies and recommendations, and 32 describing tools, decision support and educational materials. The appendix shows a list of published papers describing guidelines, policies and recommendations, by topic and source. Not included here are 7 additional policies and guidelines that were not listed in PubMed during the horizon scan (e.g., FDA, CMS, European Union, and UK Human Genetics Commission).

Table 2 also shows specific examples of the types of translational research publications by category.[7–14] More than three-fourths of these publications (n=399) addressed a specific genetic test or other health application; almost half of these (n=180) were related to cancer. The next-largest categories were hereditary disorders (21%), cardiovascular disease (11%) and birth defects (6%). Figure 1 summarizes application-specific publications by indication, along with the proportion in each group related to cancer.

Cancer represented 45% (180/399) of all articles referencing a specific genetic test or genomic technology in the T2–T4 space. One third of cancer genetic testing and genomic technology articles were related to risk assessment, followed by 19% therapeutic, 18% diagnostic, 16% prognostic, 7% preventive, and 2% population screening, with the remaining 4% addressing a combination of these. Germline testing (including utilization of family history tools) was the focus in 63% of articles addressing cancer genetic testing and genomic technologies. Somatic testing represented 36%, including 5 articles that overlapped both germline and somatic testing. Forty nine percent (88/180) of the cancer genetic testing and genomic technology articles were classified as T2 and fifty one percent (92/180) were classified as T3.

Family history tools and methods represented 7% of all articles in our collection, sub-categorized under T2 (n=10) and T3–T4 (n=25). Sixteen percent (n=82) of all articles addressed pharmacogenomic testing. Almost half of the pharmacogenomic articles were cancer-related.

DISCUSSION

In this brief report, we present baseline data on an ongoing horizon scanning by the CDC Office of Public Health Genomics, in collaboration with NCI, of the translational genomics research scientific literature. This public health surveillance activity identifies promising genomic applications for clinical practice as well as knowledge gaps that necessitate additional research. Before commenting on these findings, it is important to acknowledge the limitations of this analysis. First, in spite of our systematic effort to capture the pertinent literature, our PubMed queries had imperfect sensitivity and specificity. Although we have steadily improved specificity through manual curation by multiple reviewers, it is more difficult to quantify accurately the number of missed items. These baseline data can be used to continue to improve search capacity using machine learning tools. We will also continue

to refine the use of online search tools to capture research that is not published, or is published only in abstracts from scientific meetings, websites or online databases, or the "grey" literature. During the one-year period we analyzed, such searches identified 15 additional items, including the 7 additional guidelines and policies). These are probably only a subset of those discoverable online. Finally, we should note that publications in a given year represent the results of research initiated in prior years. To feel the pulse of translational research in genomic medicine, it is important to integrate these analyses with existing databases of clinical trials, genetic testing information, and ongoing research funding by the NIH and other institutions.[5]

We present these data as a baseline survey of post bench to bedside translational research in genomic medicine. They provide a starting point for future horizon scanning and a foundation for future enhancements as suggested above. This research represents only a small fraction of publications in human genetics and genomics. While we cannot get an accurate estimate of the denominator for such research during the period of horizon scanning, a search of PubMed for genetics and genomics research in humans yielded almost 95,000 published articles in 2012. Therefore, we estimate that our number of T2–T4 publications presented here are about half a percent of all published human genetics and genomics research. These data are consistent with previous analyses conducted in the 2000's for general human genetics research and specifically for cancer.[4,5] It is not clear what percentage of all genomic research should be distributed across T2, T3, and T4, as genomic medicine is still a rapidly moving discovery field. As the field matures we expect an increasing proportion of research and publications to be conducted in later phases of translation.

It is interesting to note that, even in the rapidly developing field of genomic medicine, 38 articles describing guidelines, policies and recommendations were published in a single year (Appendix). These articles covered a wide range of topics including newborn screening, prenatal testing, pharmacogenomics, cancer and other fields. Surveillance efforts such as the one presented here will become even more important in the near future, as additional guidelines and recommendations are developed for new genomic applications.

The CDC Office of Public Health Genomics (OPHG) continues to track new or emerging health applications of genomic research through the GAPPFinder,[15], which is an integral part of an online genomic applications in practice and prevention knowledge base (GAPPKb).[16] As part of GAPPKb, we classify genomic applications according to the maturity of evidence and readiness for use into routine clinical practice (according to a three tier classification system).[17] These efforts, along with the newly launched NIH Genetic Testing Registry[18] will help capture, over time, a more complete picture of the existing evidence on validity and utility of emerging genomic applications and the body of T2–T4 research that supports their use in practice. This evolving body of information will inform researchers, practitioners, patients, as well as policy makers.

In summary, continued horizon scanning helps identify and monitor translational research that addresses the evaluation, implementation, and health impact of genomic applications. An especially important area is cancer prevention and treatment, where some of this

research funded by the National Cancer Institute is already in progress.[19] We also expect that recent funding by the National Human Genome Research Institute for pilot demonstration projects[20] will increase the amount of information available for informed decision making on implementation and impact of genomic medicine. Other stakeholders and organizations, private and public are likely to benefit from increasing emphasis on translational research over.[21]

The importance of translational research in genomic medicine beyond the bedside cannot be overemphasized. Relevant research questions in this area need to be asked and subsequently responded to with appropriate funding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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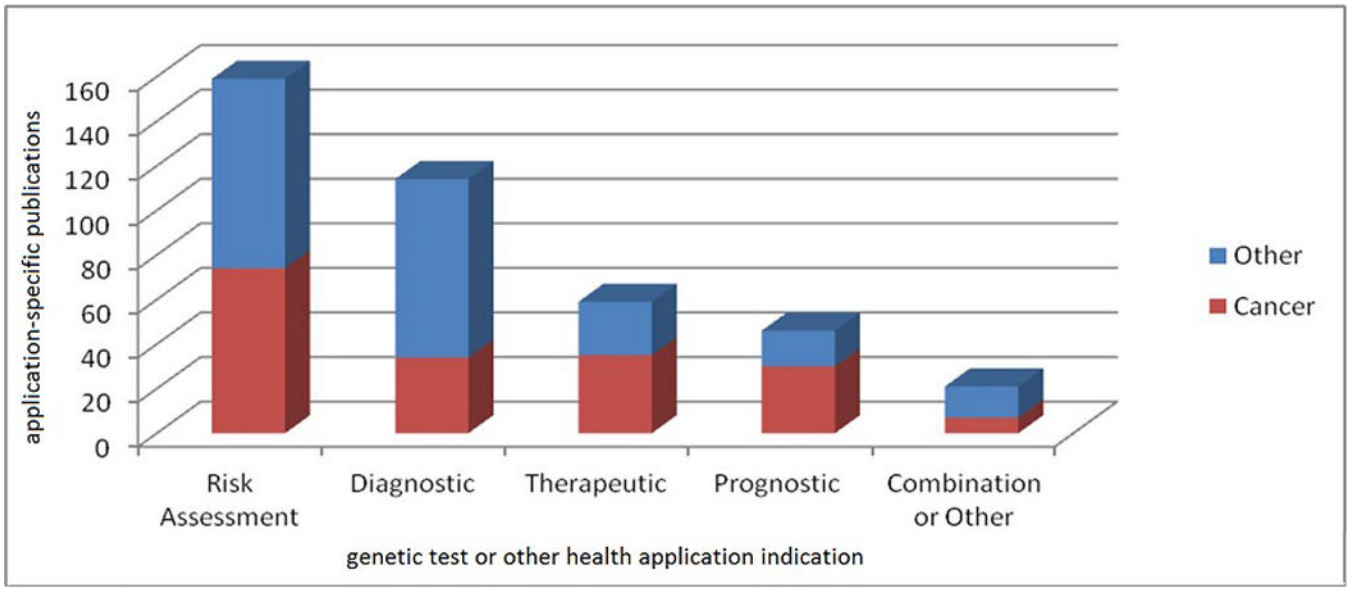

Figure 1.

Horizon Scanning Publications that Addressed a Specific Genomic Test or Health Application, by Indication, with Proportion Related to Cancer (May 16, 2012–May 15, 2013)

Table 1

Classification and Examples of Products Identified by Horizon Scanning for the CDC *Genomics and Health Impact Weekly Update* showing translational phase groupings by product type.

	T0/T1 **Discovery, characterization and development**	**T2** **Evaluation of tests and interventions**	**T3/T4** **Implementation in practice and programs**
Original Studies (A)	GWAS, biomarkers, proposed new applications	clinical trials, clinical cohorts, new data on analytic or clinical validity	studies generating new process or outcome data from clinical populations, surveillance
Research Synthesis / Modeling / Meta Analysis/ Systematic reviews / Narrative reviews (B)	Meta analysis & systematic reviews of gene-disease associations	Evidence reports	cost-effectiveness analyses, national program evaluation
Guidelines / Policies / Recommendations (C)	new nomenclature, data sharing, publication standards	Clinical practice and professional guidelines	Electronic health standards, reporting requirements, ethical standards
Tools/ Methods / Training / Education / Decision Support (D)	research road maps, databases, software, training tools	modeling methods, databases, methods for systematic review	clinical algorithms, provider and patient education materials

Table 2

Number of Publications and Specific Examples from Horizon Scanning for the CDC *Genomics and Health Impact Weekly Update*, May 16, 2012 through May 15, 2013.

	T2 (what works?)/example reference	T3–T4 (how is it implemented and is it working?)/example reference	Total
Original Research	106 (a)	206 (b)	312
Knowledge Synthesis	83 (c)	40 (d)	123
Guidelines/ Policies Recommendations	27 (e)	11 (f)	38
Tools/ Methods/Training/ Education/ Decision Support	8 (g)	24 (h)	32
Total	224	281	505