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Measuring the chronology of the translational process of molecular genetic discoveries

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Abstract

Background: The process of technology validation and transfer of new molecular diagnostic tests towards the clinic faces challenges and needs to be improved. There is no empirical measure of the chronology and pace of technology transfer of molecular genetic discoveries.
Methods: We studied these for 29 molecular genetic test discoveries in order to (1) provide estimates of the timeframe between discovery of a clinical application and complete clinical implementation, and (2) compare the trajectories between different new tests to identify common patterns. We identified 11 publicly available "timestamps" for the technology transfer process ranging from discovery of the marker to use in a clinical setting. For each test selected, we searched public databases to identify available timestamps and dates. We plotted and compared trajectories of individual tests, including chronology.
Results: We show that there is much variability in the chronology of transfer between biomarkers. The median time between discovery of the marker and availability of the clinical test was 9.5 years (minimum 1). There was a median time of 18 years between test discovery and FDA approval (minimum 7 years), and it took a median of 17 years between discovery and the availability of a certified reference material for the 10 assays that have one (minimum 9 years).
Conclusions: We conclude that new molecular genetic tests take significant time between discovery and clinical implementation, and that further work is needed to pinpoint key factors, including policy and organization factors, that may allow for improving and streamlining this process.

Keywords: genetic testing; innovation; technology transfer; translational research.

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Introduction

Since the completion of the Human Genome Project in 2001, and the HapMap Project in 2006, the pace of genetic discovery has been exponential [1, 2]. These projects have shown that the genome is a significant determinant of health [3] and response to healthcare [4], and that most diseases have a causal genetic component, thus creating expectations that genetic discoveries will strongly impact healthcare [5, 6]. Seventy percent of medical decisions rely on laboratory results [7, 8] and genetic innovations are foreseen as major sources of diagnostic and prognostic information during the present century [4, 9, 10]. However, developed countries do not efficiently deliver medical innovations to their population [11, 12], especially new gene-based biomarkers of disease derived from the human genome project [13–15]. According to the Foundation for Genomics and Population Health, although genomic science is in a "robust state", "progress is dramatically slower in evaluating the clinical and public health relevance of these scientific advances and in developing systems for effective translation of validated tests and interventions into clinical practice" [16]. We therefore must improve our understanding of the process of transferring genetic and genomic innovations from "bench to bed side" [17–21]. It has been documented that it takes on average 17 years for a scientific discovery to reach routine clinical use [22]. In order to inform the translational process for molecular diagnostic tests, we have studied the chronology and pace of technology transfer for 29 different molecular genetic test discoveries with the objectives to (1) provide estimates of the timeframe between discovery and complete clinical implementation, and (2) compare the trajectories between different new tests to identify common patterns and bottlenecks.

Materials and methods

We first developed a list of 11 publicly available "timestamps" for the technology transfer process (Table 1) and identified 29 widely used molecular genetic tests with different characteristics of mode of inheritance and clinical indications (Table 2). Most of the tests concerned one specific gene involved in one or more pathologies (e.g. *FMR1* and *APOE*), however, we also included two cytochromes P450 markers (*CYP2D6* and *CYP2C9*) used to determine drug response, a panel of microsatellite instability (HNPCC MSI) associated with hereditary non-polyposis colorectal carcinoma as well as a genomic test for non-invasive prenatal screening for fetal aneuploidies (NIPS). In addition the markers could be categorized as follows: autosomal dominant (*LDLR*, *RB1*, *F2*, *APC*, *DMPK*, *MSH2*, *RET*, *HTT*, *HNPCC MSI*, *BRCA1*, *F5*, *MLH1*, *BRCA2*, *MSH6*); autosomal recessive (*HBA1*, *HEXA*, *CFTR*, *LPL*, *SMN1*, *HFE*, *FXN*); X-linked (*DMD*, *FMR1*); predictive (*APOE*, *HTT*); pharmacogenetics (*CYP2D6*, *CYP2C9*, *MTHFR* and *TPMT*); screening (NIPS). For each marker, a search was undertaken in the indexed databases and websites of Health Technology Assessment (HTA) agencies, professional associations, medical genetics information resources and biotechnology companies. The search covered the period anterior to December 31st 2017. A list of the databases searched is presented in Table 3.

Results

A long and heterogeneous translation process

Figure 1 shows the chronology of each available timestamp for the 29 markers in relation to time expressed in years. The figure is arranged so that the top marker was the latest discovered and the bottom marker was the first discovered. For 21 out of 29 cases, the discovery of the marker was almost coincident with the discovery of the marker-disease association (not shown), suggesting that the marker was discovered because of its pathogenic role.

Table 1: List of publicly available timestamps for technology transfer.

Association marker-disease published
Patent application for molecular test
Commercial availability of analyte-specific reagents kit
FDA or CE approval of test kit
Meta-analysis published
Health technology assessment report published
Proficiency testing (QC or EQA) program
Reference material available
Certified reference material available
Guideline supporting use of the test
Accessibility of test as per Healthcare Common Procedure Coding System Codes (USA), Ontario or Québec test repertoires

In six cases, at the end of data collection, there was still no FDA or CE approved marketed tests available, indicating that in the great majority of cases that we studied, the identification of the marker led to the development of a test for the condition. Figure 2 shows a box-and-whisker plot of the time taken for each timestamp where the dot indicates the mean. The graph shows that it takes a median of 4 years after the discovery of the marker-disease association for the patents to be awarded and guidelines to be published; a median of less than 5 years for quality control assessment programs to be available, 9 years for accessibility and 9.5 years for marketing of the test; a median of 10 years for publication of HTA studies and meta-analyses; availability of reference material takes 1 more year; and a median of 18 years for availability of FDA- or CE-approved test and 17 years for a certified reference material (although for this last timestamp only 10 tests have reached this stage). The test that was translated with the smallest time lag is NIPS, with almost half the time observed for other tests.

Discussion

The main observation emerging from our analysis is that there is heterogeneity in the process of translation from discovery to clinical application between the markers studied. Indeed, all timestamps were not present for all tests, they were also or exactly in the same order and the delays between each timestamp were different. Another observation is that in terms of timeline, the translation process remains very long, with nearly 10 years before a test is marketed, and more than 18 years for a FDA- or CE-approved test. Factors that may influence this timeline include: year of discovery of the marker, strength of the link between test result and clinical validity, potential for improved health care, demonstration of clinical utility (in jurisdictions where health technology assessment is mandatory prior to implementation and coverage), funding (or reimbursement) by the health care system or health care insurers, easy interpretation of test result by the physician, laboratory constraints (such as test complexity, increased regulation of laboratory developed tests), marketing of the test, ethical considerations such as social acceptability, and lobbying by patients associations. Figure 1 shows that the most recent discoveries have a shorter timeline than the oldest. Although the numbers presented here are not sufficient to establish the causality of such an observation, technology improvements in the field of molecular diagnostics

Table 2: List of tests/markers and corresponding pathologies or role in treatment.

Marker name	Abbreviation	Pathologies or role in treatment
Adenomatous polyposis coli	*APC*	Familial adenomatous polyposis and APC-associated polyposis conditions
Apolipoprotein E	*APOE*	Alzheimer disease-2 and hyperlipoproteinemia type III
Breast cancer 1 DNA repair associated	*BRCA1*	Breast and ovarian cancer
Breast cancer 2 DNA repair associated	*BRCA2*	Breast and ovarian cancer
Cystic fibrosis transmembrane conductance regulator	*CFTR*	Cystic fibrosis
Cytochrome P450 family 2 subfamily C member 9	*CYP2C9*	Drug metabolism
Cytochrome P450 family 2 subfamily D member 6	*CYP2D6*	Drug metabolism
Dystrophin	*DMD*	Duchenne and Becker muscular dystrophies
Myotonica-protein kinase	*DMPK*	Myotonic dystrophy type I
Coagulation factor II, thrombin	*F2*	Thrombosis and dysprothrombinemia
Coagulation factor V	*F5*	Thrombophilia due to factor V Leiden or activated protein C resistance
Fragile X mental retardation 1	*FMR1*	Fragile X syndrome and premature ovarian failure
Frataxin	*FXN*	Friedreich ataxia
Hemoglobin subunit alpha 1	*HBA1*	Alpha thalassemia
Hexosaminidase subunitalpha	*HEXA*	GM2 gangliosidoses including Tay-Sachs disease and GM2 activator deficiency
Hemostatic iron regulator	*HFE*	Hereditary haemochromatosis
Huntingtin	*HTT*	Huntington's disease
Low density lipoprotein receptor	*LDLR*	Familial hypercholesterolemia
Lipoprotein lipase	*LPL*	Many disorders of lipoprotein metabolism including type I hyperlipoproteinemia and familial lipoprotein lipase deficiency
MutL homolog 1	*MLH1*	Hereditary nonpolyposis colorectal cancer type 2 or Lynch syndrome II
MutS homolog 2	*MSH2*	Hereditary nonpolyposis colon cancer type I or Lynch syndrome I
MutS homolog 6	*MSH6*	Hereditary nonpolyposis colorectal cancer type 5
Hereditary nonpolyposis colorectal cancer microsatellite instability test	HPNCC MSI	Hereditary nonpolyposis colorectal carcinoma syndrome and nonhereditary colorectal carcinoma
Methylenetetrahydrofolate reductase	*MTHFR*	Methylenetetrahydrofolate reductase deficiency
Non-invasive prenatal screening for fetal aneuploidy	NIPS	Trisomy 21, 18, and 13
RB transcriptional corepressor 1	*RB1*	Childhood retinoblastoma
Ret proto-oncogene	*RET*	Multiple endocrine neoplasia type IIA and IIB, Hirschsprung disease, medullary thyroid carcinoma
Survival of motor neuron 1, telomeric	*SMN1*	Spinal muscular atrophy
Thiopurine S-methyltransferase	*TPMT*	Drug metabolism, poor metabolism of thiopurines, 6-mercaptopurine sensitivity

Table 3: List of databases.

Database	Subject	Web site
PubMed	Biomedical citations	http://www.ncbi.nlm.nih.gov/pubmed/
GeneTests	Medical genetics information	https://www.ncbi.nlm.nih.gov/gtr/
GeneCards	Human genes	http://www.genecards.org/
HuGe Navigator	Human genome epidemiology	https://phgkb.cdc.gov/PHGKB/hNHome.action
Centre for Reviews and Dissemination	Research evidence in health and social care	https://www.crd.york.ac.uk/CRDWeb/
Orbit.com	Patents	https://www.orbit.com/#WelcomePage
Espacenet	Patents	http://www.epo.org/index.html
CIPO	Patents	http://www.ic.gc.ca/opic-cipo/cpd/eng/introduction.html
WIPO	Patents	http://www.wipo.int/portal/en/

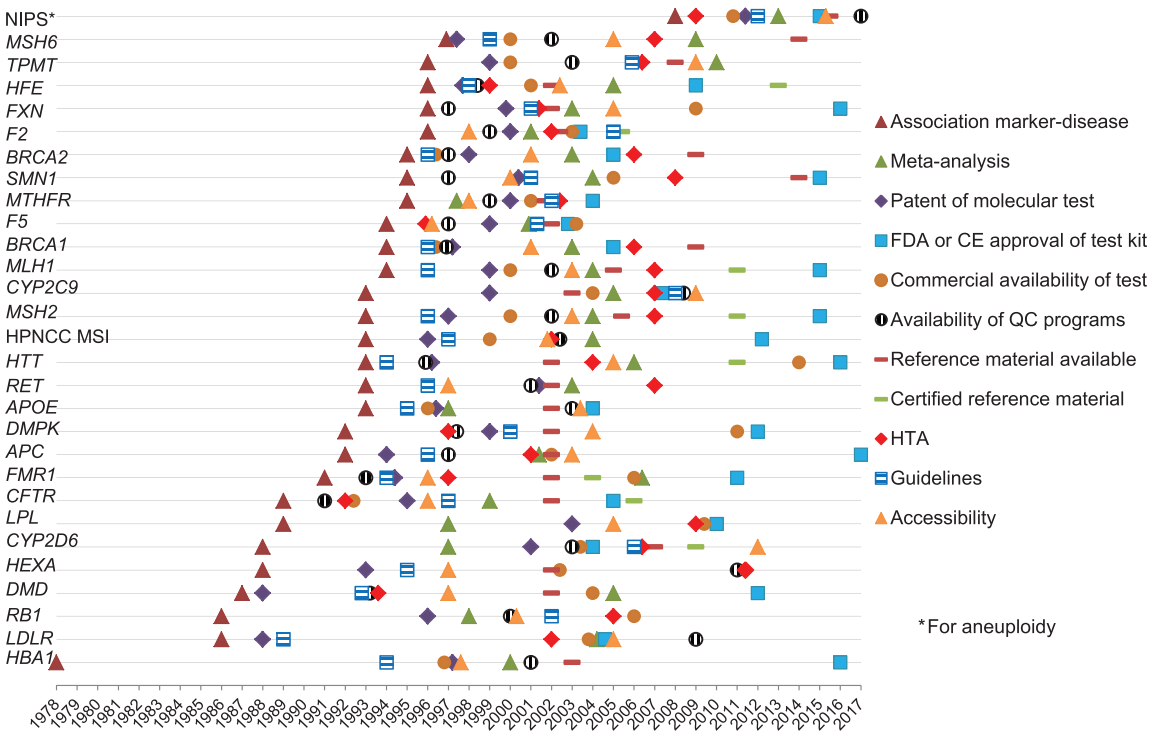

Figure 1: Chronology of public timestamps for translation of genetic discoveries into the clinic.
Chronology of public timestamps for translation of genetic discoveries into the clinic. The x-axis represents the year of the timestamps events identified for each test evaluated (y-axis, see Table 2). Each timestamp observed is shown with a different symbol (see graphic legend).

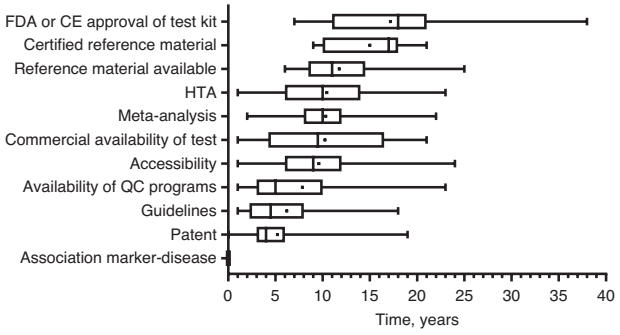

Figure 2: Box-and-whisker plot of the time taken for each test to reach specific timestamps.
Box-and-whisker plot of the time taken for each timestamp where the dot indicates the mean and the extremities of the box the upper and lower quartiles. The vertical line within the box represents the median, and the extreme lines the maximum and minimum of the values observed.

and the fact that such assays are becoming more of a commodity may contribute to this phenomenon. The reasons for the much quicker translation of NIPS may have included rapid uptake, validation and implementation by industry accompanied by strong marketing of a test that has the potential of improving significantly the safety of prenatal testing and of generating huge revenues as it is a screening test [23, 24].

One additional problem in the translation of basic research results into clinical practice is the lack of specific research funding available from public funding agencies to perform the studies providing the evidence base informing the decisions about implementing or not a new diagnostic test. There are also alternate commercialization strategies and potential barriers to commercialization that may not be related to research funding [25]. These might include the challenges of protecting diagnostic IP, the generally poor profit margins on diagnostic testing (as compared to medication), and the potential disincentive of pharma to support diagnostic tests that could limit the pool of available patients eligible to treatment. Public health systems and payers (such as health insurance companies) might also be alternate sources of funding if the test has potential for economic return, system efficiency or health improvement.

Khoury and collaborators have proposed a model in which translational research is divided into four phases: (1) development of candidate health applications; (2) evaluation leading to recommendations and guidelines; (3) implementation and integration into clinical practice; and

(4) health outcomes and population impacts [26]. A survey of research grants funded by the National Cancer Institute (USA) in 2010 indicates that only 1.7% of these grants supported the second phase or beyond [27]. An analysis of the biomedical literature between 2001 and 2006 showed that less than 3% of publications addressed phases 2–4 [26]. To further complicate the problem, due to more and more efficient technologies there is a dramatic increase in basic research findings that need replication and solid clinical validation, while some authors have raised issues concerning credibility and replication of these findings [28]. There is thus a need for a funding and research strategy to improve the systematic replication, evaluation, implementation and translation of molecular genetic markers, especially in the present context and high hopes for precision medicine based on genomic applications in health [24, 25, 29, 30].

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