INTERVIEW

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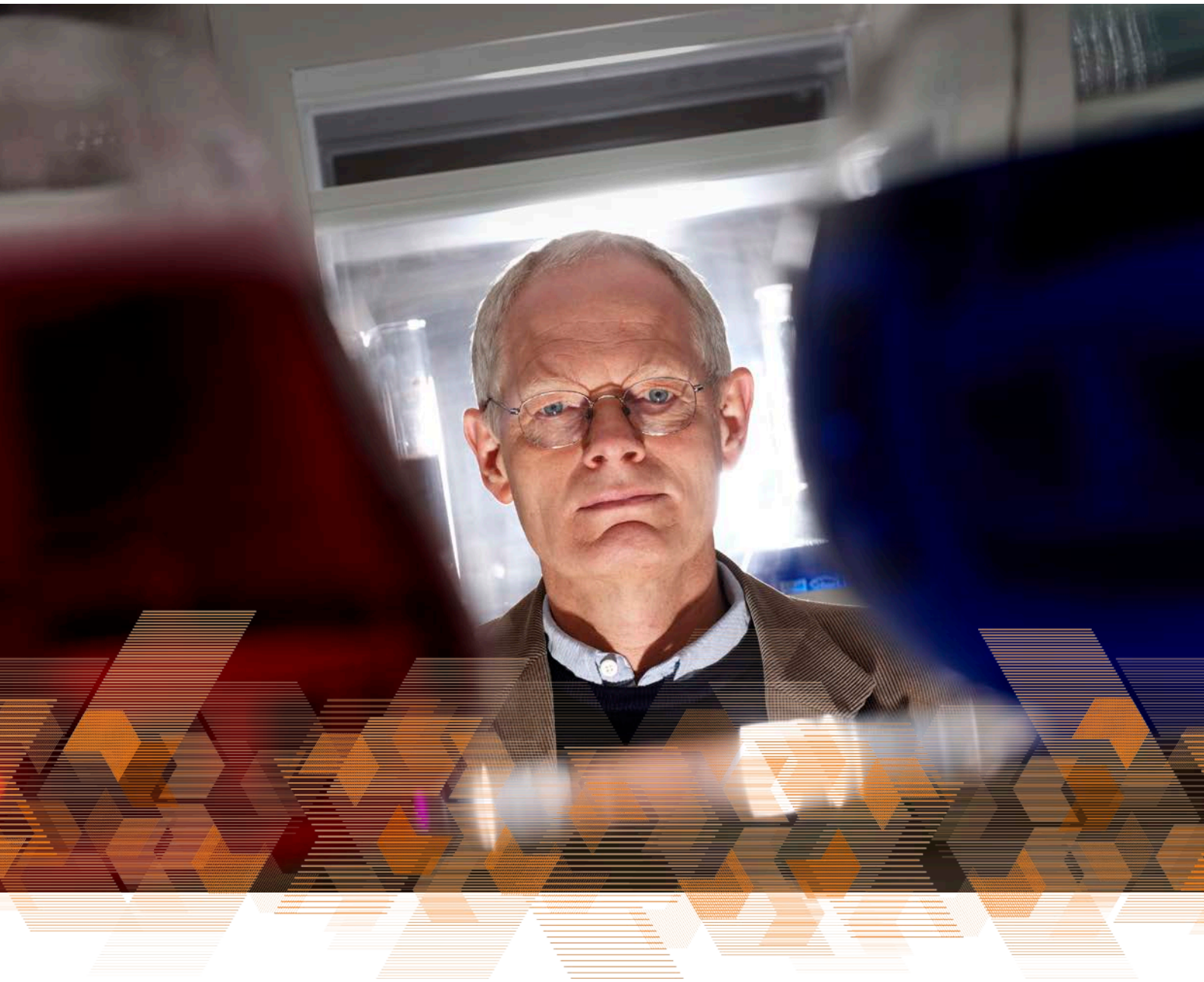


THE "GATEKEEPER" OF PRECISION MEDICINE EVOLVES.

Drug-diagnostic codevelopment can lead to a streamlined approval strategy, but will need to change in the future.

ELSEVIER

As we learn more about the biology of disease, the construct "one test, one drug" will no longer be sustainable.

"...packaging a diagnostic with one drug may no longer be realistic; instead, we may need a networked approach involving multiple drugs."

Dr. Jørgensen has been involved in precision medicine since 1999 and has written several thought-provoking articles on the topic. He has observed this paradigm shift in pharmacotherapy roar through initial hype, wane in interest, and then settle into a steady transformation in the development of new medicines built around the understanding that diseases and patient populations are heterogeneous. Dr. Jørgensen is a consultant for drug developers and a driving force behind companion diagnostics, which, in his own words, are "a kind of 'gatekeeper' in relation to which patients should be treated with the drug in question." In this interview, Dr. Jørgensen talks about the implications of this gatekeeping role and the future of companion diagnostics.

YOU ARE A STRONG PROPONENT OF THE DRUG-DIAGNOSTIC CODEVELOPMENT MODEL WHERE COLLABORATION BETWEEN DEVELOPERS OF A DRUG AND DEVELOPERS OF A DIAGNOSTIC THAT IDENTIFIES PATIENTS FOR THAT DRUG RESULTS IN A COUPLED, AND AT TIMES EVEN SPEEDIER, APPROVAL OF BOTH. WHAT DOES THIS MODEL LOOK LIKE IN PRACTICE?

This co-development model was inspired by the simultaneous FDA approval of the breast cancer medication trastuzumab (Herceptin®, Roche/Genentech) and the immunohistochemical assay for HER2 (HercepTest®, Dako) in 1998. It was also the FDA that first initiated a discussion about drug-diagnostic codevelopment with a 2005 publication where they outlined several important issues for the establishment of routine coupled approvals. Ideally, a drug developer begins working with an assay developer during the discovery and preclinical phases of a drug development program (Figure 1). Starting from a biomarker hypothesis that the assay developer uses to establish a prototype diagnostic, there is a continuous exchange of information between the two parties. The drug developer uses the prototype diagnostic to plan and conduct early clinical trials. The assay developer uses information from clinical efforts to assess the predictive characteristics of the biomarker and establish the appropriate cut-off for patient inclusion, among other things. A continuous and structured dialog between both parties is essential. It should be said, that this early collaboration and iterative exchange is not always reality, however, it is the ideal relationship under which a codevelopment becomes robust and has greater chances of success.

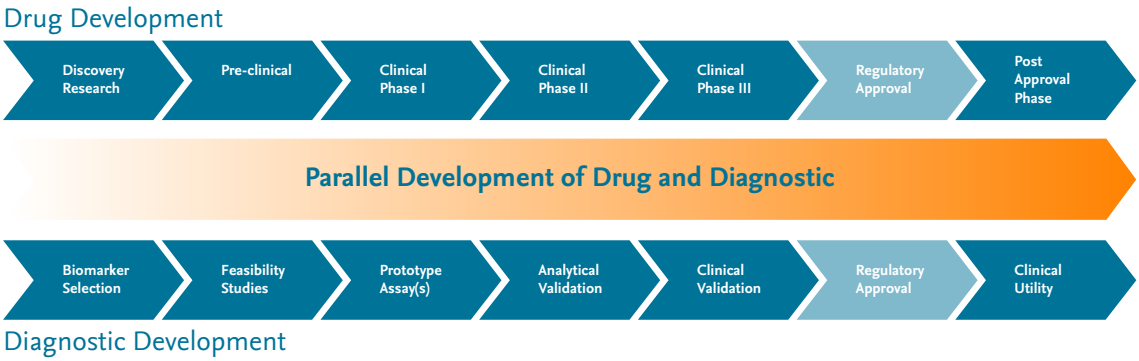


Figure 1. The drug-diagnostic codevelopment model builds on a two-way dialog between drug and assay developers. Early collaboration between the two parties coordinates development efforts for drug and diagnostic assay, which results in a strong regulatory approval strategy.
Adapted from an original design by Dr. Jan Trøst Jørgensen.

THE REGULATORY APPROVAL OF A NEW DRUG IS A RESOURCE AND TIME-INTENSIVE ENDEAVOR, OFTEN TAKING SEVERAL YEARS TO ACCOMPLISH. ADDING A DIAGNOSTIC ASSAY TO THE PICTURE SEEMS TO COMPLICATE MATTERS. WHAT ARE THE ADVANTAGES IN CODEVELOPING DRUG AND DIAGNOSTIC?

We have to bear in mind that companion diagnostics is in its infancy and codevelopment programs experience all the accompanying growing pains. There is, for example, discord between the regulatory status and consequent requirements of diagnostics in general and the "gatekeeper" role of a companion diagnostic. This is something Daniel Hayes from the University of Michigan, Ann Arbor, and myself have been pointing out for some time. Under our current vision of stratified medicine, where a patient population is subdivided — stratified — into groups based on biological characteristics that are relevant to an individual's response to a drug, a companion diagnostic is the gatekeeper that determines which patients should be treated with a given drug. As this pivotal node in a patient's therapy, the diagnostic assay greatly impacts therapeutic outcome and should be subjected to the same level of regulatory requirements as the drug it accompanies.

Having said that, the link between drug and diagnostic at the point of therapy extends back to the development and approval process, and this can be very advantageous. Let's start with the use of the prototype diagnostic to plan and conduct phase I and phase II clinical trials. Information from these stages may feed back to further optimize a compound. Also, the data from these trials are used to establish the cut-off for patient inclusion in phase III trials and, ultimately, clinical use after approval. The right cut-off plays a critical role in the approval strategy for the drug-diagnostic pair. This is a highly complex analysis that can take months to complete and balances relevant biology (hypothesized drug mode of action, disease mechanisms, observed response rates) with the sensitivity and specificity of the diagnostic and several clinical trial design aspects that impact demonstrating the efficacy of the drug. In other words, the codevelopment leads to a better informed and streamlined regulatory approval strategy. Just 5 or 6 years ago, drug developers were hesitant to engage early with diagnostic developers, partly because of the uncertainty of success in drug development. Sometime they would first contact a diagnostic developer after not achieving the targeted efficacy in phase II trials. Now we see companion diagnostics entering the framework much earlier and the result of this front-ended collaboration can be a fast-tracked approval, like that of the lung cancer drug crizotinib (Xalkori®, Pfizer) and its companion diagnostic (VYSIS® ALK Break Apart FISH Probe Kit, Abbott). Thus, uncertainty about a drug should not stop you from working toward a companion diagnostic, because it could rescue your drug!

ARE THERE DRAWBACKS TO THE DRUG-DIAGNOSTIC CODEVELOPMENT MODEL?

There are drawbacks and interestingly, these arise precisely from the main task of the diagnostic: to identify the patient subgroup that responds to the drug. The standard of clinical trial design used in the drug-diagnostic codevelopment model is the enrichment study design. Here only the patients who test positive with the diagnostic are randomly assigned to be treated with the tested drug or with a comparator. In some cases even, all positive patients are assigned to be treated with the tested drug – no randomization and no comparator. Approvals from such trials are based on remarkable response rates of 50% and higher, where there is little room for doubt that the use of the diagnostic and the drug had a positive therapeutic outcome for the patient. However, the trial design means that the drug is tested on a small number of patients. In the case of crizotinib, it was only 255 ALK-positive patients with non-small cell lung cancer. Safety data about the drug are therefore limited and the FDA rightfully mandates in such cases post-approval data to address the missing information. The benefit is that an obviously effective drug is available to physicians and patients as quickly as possible and this works well for oncology, where most would choose an experimental or newly approved drug over chemotherapy. However, the risk to the drug developer is latent. Another drawback of these trial designs is that by leaving out the patients who tested negative with the diagnostic, the trial no longer provides data needed to determine clinical sensitivity and specificity of the diagnostic. We know that the diagnostic has clinical utility — with response rates upwards of 50-60%, the companion diagnostic of crizotinib

certainly identifies patients who benefit from the drug — but we know nothing about its sensitivity or specificity. Were patients who could have benefited from crizotinib not identified? What patients definitely do not benefit from crizotinib? Those answers will need to come as more data are collected in continued post-approval trials. A final drawback worth mentioning is the endpoint measured in these trials. Response rate is used as a surrogate of the truly meaningful endpoint: survival. Meta-analyses for an indication such as non-small cell lung cancer seems to show that response rate is proportional to survival, but only long-term data can tell us if a high response rate actually corresponds to extended survival.

WHEN WE LOOK AT THE LIST OF FDA-APPROVED COMPANION DIAGNOSTICS, TWO PATTERNS EMERGE. ONE IS THAT THERE ARE REALLY VERY FEW OF THEM — 20, AS OF DECEMBER 2014. THE OTHER IS THAT 50% OF THE APPROVED COMPANION DIAGNOSTICS ARE LINKED TO HERCEPTIN AND OTHER HER2 TARGETED DRUGS. CAN YOU EXPLAIN THOSE PATTERNS?

I myself have been a bit surprised by the low number of companion diagnostics and the rather slow transformation towards stratified medicine that we have witnessed. However, I think that this is a changing trend and we will have a "ramp up" in next years as we learn more about the molecular biology of diseases and as more drug developers recognize the value of medicines targeting specific biological subgroups of patients. Perhaps the second pattern you mention mirrors this change. Herceptin has been around for a long time, so we understand the biology quite well. Each new companion diagnostic associated with the drug and other HER2 targeted drugs like pertuzumab (Perjeta®, Genentech) and ado-trastuzumab emtansine (Kadcyla®, Genentech) may emerge for commercial reasons, but also because of an improved understanding of the mechanisms of cancer, the introduction of better assay technologies, or the approval of the drug for new indications, such as gastric cancer. I think, however, that it is fair to say that the quantity and diversity of companion diagnostics entering the clinical setting is and will continue to rise.

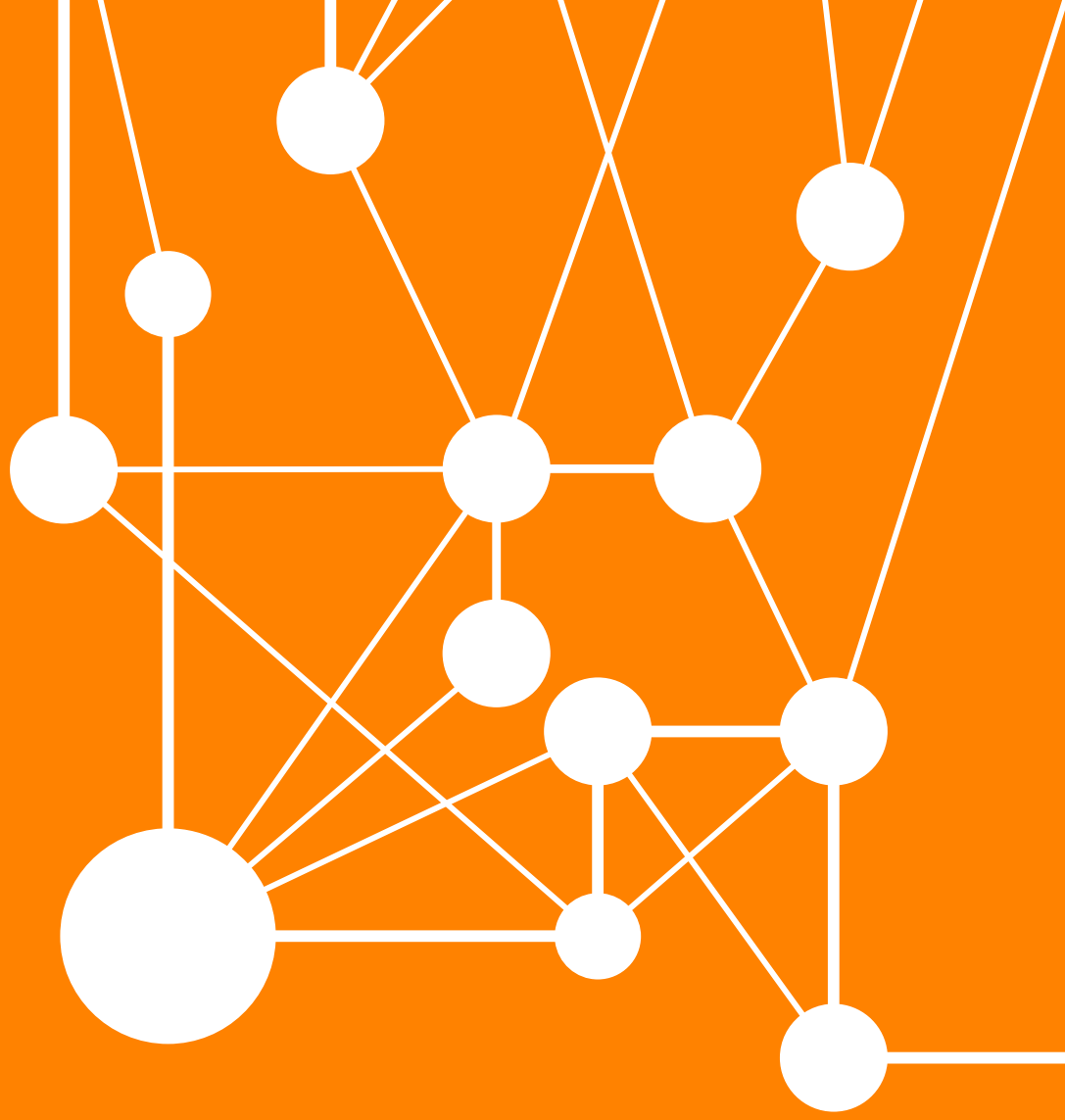
"We also need not be naive about the long path ahead. We need more drugs. We need a far better understanding of the molecular mechanisms underlying cancer and all other diseases that can benefit from precision medicine. And while our tools are getting better and we are getting smarter, what lies ahead is still small steps and serial improvement of therapies. But we are seeing progress. We are moving forward toward truly personalized medicine."

WHAT IS THE FUTURE OF COMPANION DIAGNOSTICS?

This question brings us back to the drawbacks I mentioned previously. The drug-diagnostic codevelopment model currently operates under the assumption of "oncogene addiction" — the postulation that tumors rely on a single dominant oncogene of growth and survival so that inhibiting that oncogene or pathway is sufficient to halt tumor growth. The result is a "one test, one drug" construct. There is mounting evidence that oncogene addiction is, at best, a transitory condition and tumors change over time. We already see resistance development in most patients on some of these targeted medicines. For example, ceritinib (Zykadia®, Novartis) is another lung cancer drug that received rapid approval and is indicated for patients who progress on crizotinib, that is, that have developed resistance to this drug. As we learn more about the biology of disease, we can characterize patient subpopulations in increasing detail and as a result, drugs will target increasingly smaller groups of patients. Such precision in therapy is a welcome prospect of truly individualized management of disease, but the construct "one test, one drug" is not sustainable under those conditions. From the physician and patient perspective, this construct would mean an inordinate number of tests to determine the right therapy. From a drug developer perspective, demonstrating drug efficacy with increasingly smaller patient sample sizes will become very difficult or impossible.

In my view, the only solution is a new multimodal approach. For diagnostics, I think that will look like multiplexed panels or arrays that deliver information on multiple relevant biomarkers. Next-generation sequencing has the potential to play a big role here but it will not be the only platform. Diagnostic information can also come from proteins, metabolites, or even functional imaging. The result of this is that packaging a diagnostic with one drug may no longer be realistic; instead, we may need a networked approach involving multiple drugs. The bottleneck is the burden on drug developers. We might know all the right disease-causing mutations, but we do not have the arsenal of drugs. I also believe that clinical trial design will have to evolve. We will need to step away from the restrictions of controlled, randomized trials and develop more flexible and adaptive structures, including open observational studies, that enable cooperation and data sharing. I can envision a knowledge-producing system that spans multiple clinical trials. Patient profile and trial outcome data must meet predetermined minimum requirements to be compiled in the system but can then be used to generate analyses comparing groups between and among different participating trials. I do not see this as a purely academic exercise but one that can also benefit drug developers. Such a design would allow them to test their drug on a small target group but capitalize on the data in the system as a whole to produce significant analyses. Furthermore, drug combinations can more easily be tested under such a framework.

We need not be naive. Competition will be an issue for such a model. However, we are already seeing changes in mentality that can lead down this path. Basket trials are an example, where patients are included in a trial based on their genetic profile and not on the type of cancer they have (lung, breast, colon, etc). This is a retreat from the histological classification of cancer that has prevailed for decades but has proven to be less informative than a classification based on molecular characteristics. We also need not be naive about the long path ahead. We need more drugs. We need a far better understanding of the molecular mechanisms underlying cancer and all other diseases that can benefit from precision medicine. And while our tools are getting better and we are getting smarter, what lies ahead is still small steps and serial improvement of therapies. But we are seeing progress. We are moving forward toward truly personalized medicine.



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