

Biochips: Bright Future in Clinical Dx?

M. Kohl¹, S. Koch², M. Keller³ and H.P. Deigner^{1,2*}

¹Furtwangen University, 78054 Villingen-Schwenningen, Germany

²Fraunhofer Institute IZI, Leipzig/EXIM Rostock, 18057 Rostock, Germany

³Clinics Essen, Centre for Pediatrics, 45147 Essen

Biochips play an established important role in research on disease biology and systems biology while an increasing number of clinical applications is emerging. What about the future of biochips in medical routine? The term biochip as used by us in this editorial is confined to chips in DNA/RNA analysis, just for sake of brevity, not implying any judgement.

We hypothesize that the future will bring a routine use of biochips in diagnostics and provide arguments to support our view. We comment on technological and data analysis aspects, also with regard to 3rd generation sequencing, and point out remaining challenges. We foresee an increasing application of biochips in the clinic and beyond, in the hand of practitioners. What are the reasons to justify the optimism about biochips potential to accelerate not only the understanding of the biological basis of diseases but to develop into an integral part of medicinal diagnostics?

While the development of individualized therapy will be slower than predicted by many euphoric stakeholders, however, it is a trend which is inevitable. (Figure 1) Demonstrates the continuously growth of clinical applications of biochips, in clinical studies and disease biology. Biomarker identification and biochip applications build the basis of individualized therapy, precise diagnosis, and accurate sub-classification of disorders, all essential prerequisites for targeted treatment and for directing therapy.

In drug development biomarker applications also comprise patient stratification to identify subjects to be enrolled in studies and for improved design of clinical trials [1] thus reducing effort, expenses and time. While this will raise success rates in treatment, speed up drug development and bring the appropriate therapy to those subjects benefiting most of it, targeting will at the same time reduce the total number of administrations. It is quite clear, however, that this unavoidable market splitting does not meet the commercial interests of drug companies.

Thus being in the primary interest of the patient rather than in that of big pharma and diagnostics companies, we believe that the pace of advancements in Personalized Medicine can actually be stimulated by activities of patient's representative organisations. Informed patients as sample donors involved in therapy decision-making are in a strong position to support developments toward optimal individualized treatment. Platforms for discussion of patients' representatives with biomedical researchers, drug-, diagnostics companies and biobanks like e.g. the European Society for Biopreservation and Biobanking (ESBB, <http://www.esbb.org/>) will catalyze this trend. Accordingly, we are convinced that applications of biochips in clinical diagnostics will grow along with therapy individualisation and with demonstrated successful samples.

Some challenges, however, remain to be coped with prior to reliable routine use. Issues to be addressed comprise, in particular with regard to the high-density biochip formats used in the screening phase, reproducible/automated preanalytics, standardisation, normalisation, statistics and extensive clinical validation of identified biomarker candidates. [1,2]

The microarray quality control [4] came to the conclusion that microarray results, i.e. differentially expressed genes, are reproducible and reliable. But, this is only the first part of the story. In 2005 Michiels and colleagues reported that only two of seven cancer studies with microarrays classified patients better than chance [5]; To overcome this deficiency, the FDA in 2006 launched phase two of the MAQC-project focussing on the generation of predictive models [4]. The MicroArray Quality Control (MAQC)-II study of common practices for the development and validation of microarray-based predictive models [6]. The main result was that the prediction performance was predominantly endpoint dependent where multiple models of comparable performance can be developed for a given endpoint. In particular, the study showed that simple data analysis methods often perform equally well when compared to more complicated approaches. Despite of this progress in the last five years, only 22 genomic markers so far have entered the "Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels". This might be related to the fact that it takes several years to validate a genomic biomarker. In addition, the necessary reproducibility of the data analyses is essential but hard to achieve to mention another result of the MAQC-II study.

Given the recent dramatic development in gain of power togeth-

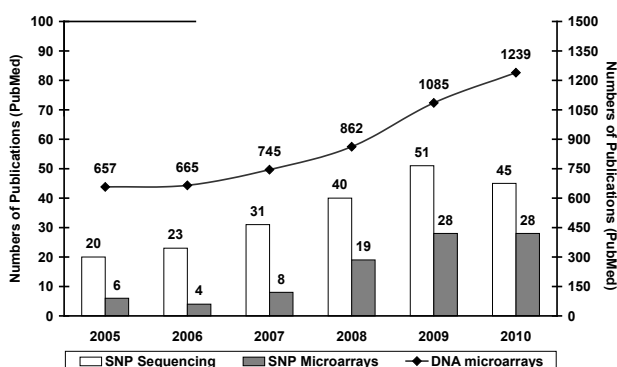


Figure 1: Trend of microarray use for human clinical sample analysis.

The total number of publications in PubMed concerning DNA microarrays for clinical sample analysis is shown (2005-2010) as well as numbers of publications for detection of Single Nucleotide Polymorphisms (SNP) as determined by sequencing or microarrays. Search terms: DNA microarrays AND clinical samples, SNP sequencing AND clinical samples, microarrays AND clinical samples.

*Corresponding author: Hans-Peter Deigner, Fraunhofer Institut IZI, Leipzig/ EXIM Rostock, 18057 Rostock and Furtwangen University, 78054 Villingen-Schwenningen, Germany, E-mail: deigner@gmx.de

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er with falling costs, 3rd generation sequencing will gain increasing importance as for analysis of SNPs and genetic disease prevalence as well as for quantitative RNA sequencing in transcriptomics. The development of guidelines for the analysis of such data, however, has just started in 2009 (MAQC-III also known as SEQC) and many problems as for quantitation, platform dependence and more require further research. Hence, we can expect about another five years from now until the analysis of RNA data will be equally well established than for microarrays.

In view of these considerations we agree with Green and Guyer [7] pointing out that these new technologies will be able to improve the effectiveness of clinical medicine not before 2020. Further, the discovery of rare risk-conferring variants involved in complex disease etiology via sequencing requires large sample sizes and improved phenotype standardisation limiting progress speed [8].

While we expect that sequencing will become the method of choice for pangenomic SNP analysis, genotype guided prevalence assessment and in transcriptomics screening, our experience suggests that a limited number of selected and thoroughly validated features is usually sufficient and frequently optimal for precise diagnosis of complex diseases in many cases. Diagnosis of complex diseases, on the other hand, requires determination of several disease-associated biological parameters and single marker diagnostics do not represent state of the art. We found that an optimal number of features, respectively probes for biomarker (e.g. transcripts of blood cells or serum metabolites) frequently lies around 10, and rarely exceeds a number of 25 [2]. Hence, not surprisingly 7 out of 15 commercialized multi-gene biomarkers for breast cancer include 21 or fewer genes [9]. The use of transcription pattern in clinical diagnostics has experienced some setbacks, initially due to technological features, frequently and still ongoing due to flaws in statistics and data analysis [10]. In view of one of the main problems of whole genome microarrays which are a large number of false positive findings, the use of microarrays with a limited number of preselected probes might be a way to improve the development of diagnostic chips. It should be noted, however, that even with such a limited number of features, statistics is not trivial and it is important to combine supervised learning methods with sophisticated feature selection procedures to achieve reproducible results.

Given the availability of clinical chemistry labs with sophisticated instrumentation and trained personnel, the need for tests actually to be performed at bedside appears limited in a clinical setting. There is, however, still an unmet need to perform on-site diagnostics in many cases, for instance to confirm a stroke at the patient's home. Biochips provide excellent formats for determining a limited number of validated molecular targets with a relative simple technology.

In sum we see plenty of evidence to forecast a bright future for diagnostic biochips. A combination of various types of biological molecules in diagnostic marker panels will open additional opportunities especially for complex diseases and sophisticated cases [2]. For instance, a combination of micro RNA and metabolite analysis, both biomolecules which can be determined from the same biofluid, plasma, promises a significant enhancement of test sensitivities / specificities in selected cases.

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