

Is Molecular Cytogenetic Diagnostics of Rare Diseases in Europe Close to Extinction

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Editorial

Molecular cytogenetic diagnostics is based on fluorescence in situ hybridization (FISH) [1] and is best suited to the characterization of chromosomal rearrangements in prenatal, postnatal and tumour cytogenetic diagnostics [1-4]. Chromosomal rearrangements detectable by molecular cytogenetics are well-known biomarkers for constitutional syndromes (e.g. microdeletion-syndromes) [5] and acquired diseases [2]. It is beyond doubt that FISH is a necessary approach among the accumulation of modern genetic laboratory tests [6]. It can be performed in metaphase and interphase, and is a quick, applicable and straightforward approach, even giving information at the single cell level and in genetic mosaic conditions, being especially valuable in tumour diagnostics [2]. It has been shown that specific questions in individualized medicine and rare diseases can only be answered using FISH-probes and probe-sets which are purpose-made in-house [1-8].

Nonetheless, molecular cytogenetic diagnostics has been in danger for several years, due to the peculiarities of many, but not all, European national health services. FISH-probes are expensive both when they are purchased ready to use from a commercial supplier and also when they are made in individual laboratories. The retail cost of one FISH probe is between 25€ and 50€ per test; if multicolour FISH probe sets are needed the price for a complete test can be up to 150€ or even more. For purpose-made, in-house FISH probes the cost of consumables, working time and testing of the probe before use in diagnostic cases will come at present to approximately the same price per test. So, when looking at the reimbursements available from public health systems in Europe, it is clear that molecular cytogenetic diagnostics is, in most countries, not profitable (Tab. 1). Beside the costs of FISH-probes considered in Tab. 1, there is also a need to cover other costs such as personnel, supply and inspections for lab equipment, microscopes, software updates and accreditation. This unfortunate situation has already restricted the options for patients needing FISH diagnostics, and especially those with indications that would be best studied by the application of multicolour FISH probe sets [3] or the use of many FISH probes consecutively or in parallel [2]. A particular mention should be made in this context of infertile couples with repeated early abortions. It is well known that in up to 5% of such couples the

reason for abortions may be a balanced cryptic translocation that is only detectable by FISH [9]. Therefore, it used to be a well-established molecular cytogenetics-based approach to use all 41 commercially available human subtelomeric probes in such couples to detect such rearrangements. However, as the cost per tested person is more than 1000 Euro for the necessary probes, this test has practically stopped being offered in Germany, for example, as each person tested means a loss of around 600€ for the molecular cytogenetic laboratory involved. This is a current example of how the logic of cost efficiency means that genetic diagnostics are regressing to the 1990s, and within the next two years the situation may deteriorate further for the majority of rare genetic diseases.

This unexpected problem was tightened by the “EU Regulation 2017/746 of the European Parliament and of the Council diagnostic medical devices (IVDR)”. IVDR was introduced to protect patients from the use of unlicensed medical products. In principle it is a good idea, introduced as it was as a reaction to the scandal of the implantation of non-medical silicone in hundreds of women after breast surgery. More precisely: with the IVDR, the rules for the approval of diagnostics were adapted to those requirements valid for medical devices, and is applies now also for genetic diagnostics.

The problem is that, from 26 May 2022 only specifically for human diagnostics certified test systems, including FISH probes, will be permitted for use in molecular cytogenetic diagnostics. Probes made in-house will only be permitted to be used if they are not commercially available. In addition, for each laboratory, their use will have to be specifically approved by a national association. This will be the TÜV-Süd (Technischer Überwachungsverein Süd, Germany), an association that has had no expertise at all up to now in the checking of genetic tests. This new regulation will also certainly increase costs for each test based on in-house manufactured as well as commercially available probes [10], and an additional reimbursement is not foreseen in health systems yet.

The laboratory of the author of this editorial (Molecular Cytogenetics Laboratory at the Institute of Human Genetics, Jena, Germany) carries out around 1500 FISH tests per year; 90% of cases come from all over Germany, and the remaining 10% are from different European countries, and even worldwide. In around 75% of the tested cases some of the more than 7000 available in-house probes are used. This is because there are mainly individual requests

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for molecular cytogenetic studies that are not covered by any commercially available FISH-probes, as unique chromosomal aberrations tend to be the rule rather than the exception in rare diseases. As soon as the IVDR is implemented in Germany as foreseen, the Jena lab of the author will need to do much more efforts to legally apply the above-mentioned in-house probes in diagnostics. In other words to meet requirements of IVDR (Article 5 §5), besides technical documentation for in-house products, one has to provide a specific and more sophisticated proof of clinical benefits, market monitoring (in-house) and risk management for every manufactured product, than it is already the case now. This will most likely be, if at all possible, very laborious, thus costly and not be refundable by any means.

Even worse, as far as we understand the IVDR will also impair and completely or possibly even block the chromosome banding analyses and tissue staining approaches used in haematology and pathology (these are tests made in individual laboratories and no commercial supplier offers complete test kits), molecular genetic diagnostics based on in-house designed primers, for example microsatellite analyses and Sanger-sequencing or individual MLPA-tests, and many other 'home made' in-house tests.

As according to EU-legislation yet no exemptions from IVDR for genetic and other tests for rare diseases are foreseen, possibly after May 2022 Europe will find itself not only without molecular cytogenetic diagnostics for rare diseases, which have been established since the 1990s as a highly reliable test for patients, but will also lose a lot of other genetic and other tests that are now standard in modern medicine. Can this really be the goal of IVDR and in the interest of patients?

Key Words:

Validation; Prognostics; Pharmacogenomics; Pharmacogenomics; Diagnostics;

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