

Do rare cancers deserve specific strategies for cancer research?



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The ongoing European Campaign Against Rare Cancers recalls that among the many problems posed by rare cancers, and rare diseases, some affect clinical research.¹ Undoubtedly, focusing on how to better organise clinical studies can help. However, we should also look at their methodology.

Organising better clinical research in rare cancers means fostering cooperation to increase the number of patients, and thereby the statistical power, of clinical studies. National and international collaborative studies can recruit numbers that would not be possible on a smaller scale. However, there is one main limitation: the clinical expertise on rare cancers is not widespread. This means that quality of care in a widely collaborative clinical trial might be suboptimal. All too often we look at the quality of clinical studies as if quality of care did not matter.² Good clinical practice rules and reviewing mechanisms mainly focus on data quality and compliance with methodological requirements. This has little to do with how treatment is done. In fact, not only the experimental treatment, but the overall quality of care is also relevant. Take, for example, a new medical therapy that causes more tumour responses. A survival benefit might result from it, provided, say, surgery is used at best. If not, the prognostic effect of the new medical therapy might be diluted, and the study could be negative for the final endpoint. Quality of care is therefore always an issue in clinical studies, and all the more so in rare cancers.

Sometimes, big organisational efforts tend to relax study inclusion criteria to further increase numbers. For obvious reasons, the temptation to do this is high in studies of rare cancers. However, by relaxing inclusion criteria the effect of therapy might be diluted further, especially if treatment should be tailored to selected subgroups. If a histological type is represented by only one patient in a clinical trial, will the quality of evidence of that study be superior to a case report? With very rare cancers, in fact, it could be that clinical decisions are based on case reports, or anecdotal evidence, even when studies are available.³ The logic of evidence-based medicine should be adapted to rare cancers. If quality of evidence only resides in numbers, patients with rare cancers would be discriminated against by their very definition.

Some methodological options, such as Bayesian approaches, could be used to improve this evidence

base.⁴⁻⁶ Clinicians are used to a Bayesian approach in medical diagnosis.^{7,8} A prior probability of disease will give rise to a posterior probability, and so forth. When clinicians see a shadow on a lung scan, they do not put a so-called frequentist question to their radiologists. If they were interested in something like a p value, the question would sound like "what probability did I have of obtaining this scan if this were not a metastasis?" On the contrary, they try to put that shadow into its clinical context. They try to understand which is the posterior probability that the shadow is indeed a metastasis. They combine a prior probability with the new empirical evidence coming from the scan. Undoubtedly, the prior probability will be influential, but compelling evidence from the new test makes it less crucial. Why should a single study, or even a single rare cancer case, not be viewed in the same way? In the case of rare diseases we need to maximise the effect of each new piece of knowledge. Why should prior knowledge, including preclinical evidence, not be formally taken into account in the era of molecularly targeted therapy? In the face of a strong preclinical rationale (eg, an activating mutation of an oncogene), even patient zero might count a lot.⁹ A no-therapy control group will be unethical as early as the second patient. In other words, a little empirical evidence might be enough to substantially update a strong prior probability, and vice-versa, of course. With a Bayesian approach to clinical research, the prior probability would be influential, all the more so if new empirical evidence is scarce. Undoubtedly, prior probability might be weak, and this is often claimed to be a major limitation. Indeed, this uncertainty might be the price we have to pay to avoid discriminating against patients with rare cancers. However, such uncertainty would be treated explicitly and appropriately, and could be challenged in its premises. It could also be incorporated in a patient-physician shared decision-making process that accommodated uncertainty.

Even after a clinical study, should we apply results derived from its average patient to any patient of ours? A patient might have a rare mutation known to be insensitive *in vitro* to a molecularly targeted agent that was proven effective as an adjuvant. However, the study population was mainly made up of patients with sensitive mutations. Should we not combine clinical with preclinical evidence, and avoid treating that rare patient? It looks

like the medical community is not prepared to behave consistently with this rare patient.¹⁰ The problem is that clinical research and clinical decision making must merge into each other. There is probably no other area other than rare diseases where the logic of current medical statistics looks so far removed from clinical decision making.

Bayesian approaches are not the only methodological option available for assessing rare cancers. Surrogate endpoints are another resource; problematic though they might be.¹¹ Looking at rare cancers is important because they are rare individually, but not collectively. The RARECARE project showed that even a conservative definition of rare cancers would see them account for as many as a fifth of all cancer cases.¹² Thus, there is good reason to work on the quality of evidence achievable in rare cancers. Common cancers are currently divided into smaller subgroups by molecularly targeted therapies, if not nosographically, then at least therapeutically. Therefore, what has until now has been a problem for the oncologist treating rare cancers could become an issue for colleagues dealing with these more common cancers. One more reason to be courageous.

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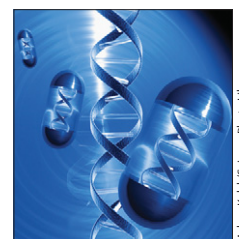
Clinical implementation of pharmacogenomics: overcoming genetic exceptionalism



After more than half a century of pharmacogenomic research, the clinical use of pharmacogenomic testing remains uncommon, despite many examples showing that inherited genomic variation causes substantial interindividual differences in drug effects. Since the sequences of pooled human genomes were made public,^{1,2} only a handful of pharmacogenetic tests have been translated into clinical laboratory tests. With the adoption of genetic non-discrimination laws,³ fewer legal arguments can be made for withholding genetic tests from medical records. We address some of the reasons underlying genetic exceptionalism, as it applies to the slow adoption of pharmacogenomics, and discuss the steps we are taking to combat this deficiency in clinical practice.

When making prescribing decisions, health-care providers must integrate multiple types of information (eg, age, concurrent medications, renal, and liver function) that are helpful, but imperfect. Pharmacogenomic information, like non-genetic variables, need not be perfect to provide useful information to the prescriber. Despite evidence linking pharmacogenomic variation with drug exposure, toxic effects, and efficacy, many clinicians, regulators, and payors hold pharmacogenetic evidence to excessively high standards.⁴

In our own practices, we have used several pharmacogenomic tests. Treatment of acute lymphoblastic leukaemia includes thiopurines, the metabolism, adverse effects, and effectiveness of which have been



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