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Norwegian Cancer Genomics Consortium: a platform for research on personalized cancer medicine in a public health system

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Although the options for personalized cancer treatments are increasing, the lack of a deep understanding of mechanistic issues is generally a limiting factor, and precise cost:benefit ratios are slow to emerge. Whereas patients and the public see the great potential, and market-driven health services have been quick adopters, many public health systems are hesitant to offer generally expensive drugs without having clear efficacy data as a base for the prioritization of limited common resources. In particular for patients and their families, this appears as a disregard of their interests, and several request their biopsies and pursue commercial services that can identify possible targets and even suggest recruiting trials. On the one hand, public health cannot stop patients from using 'alternative' treatments at their own expense, but on the other, it is sad that patients do not feel that they are well served by 'their own' health service. To be clear on this latter point, it is crucial that public health services not only focus on the newest developments, and invest in the new technologies and critically evaluate new therapies, but also that their patients get fair and good access to trials that provide hope for a cure and knowledge to the service.

On the one hand, a plethora of candidate therapeutic targets (e.g., in advanced prostate cancer [1]) and many isolated success cases have been reported, but on the other, early basket trials using targets across cancers have so far been challenging or even disappointing [2–5]. Clearly, this field is still in its infancy, and there is insufficient biological understanding of the processes and mechanisms involved, and of the specific conditions limiting responses in the individual patient. To be able to make good judgments on the deluge of scientific data and drug marketing and, thus, reasonable priorities for the health service, the service itself needs to engage heavily in research on these topics. The public willingness to pay for a health system is absolutely dependent on trust in the quality of the services provided.

Thus, the public has high expectations, patients demand the newest treatments, frequently supported by industry, the authorities are anxious about increasing costs, and the health service is increasingly pressured in terms of its cost control. As scientists, we are keen to promote the promise and opportunities, but although genome technologies are now affordable and largely routine in a research lab, we tend to underestimate the challenges involved in the equally important large-scale accumulation, quality assurance, analysis of medical information, and translating epidemiological data into treatment algorithms that are useful to the individual patient. Another challenge is the resistance to change in the health service, and the challenge of changing the understanding of 'knowledge-based medicine' from always being based on large randomized studies to new formats better suited to smaller groups of patients and more biological investigations. To meet these challenges, we need to work on at least three axes; (i) public and professional education, to disseminate a balanced understanding and, thus, expectation of the opportunities becoming available; (ii) to support oncologists and pathologists towards the wider use of genetic and genomic tumor characterization to guide treatment; and (iii) increasing the investment in research to determine how and where genome-based stratification and targeted therapies should be used.

In Norway, there are two national initiatives with such objectives, one top-down, organized by the health service, and one bottom-up organized by scientists and oncologists.

The National Collaboration Group on Health Research has identified the topic 'Individualized

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cancer treatment based on personal tumor gene profiles' as their single national priority area within cancer research (http://kreftsatsing.no). A task force, established with cross-discipline experts from all health regions, is considering how to achieve this objective in a sustainable way, and is providing advice to the health service to this end. Annual conferences have been organized to raise awareness of the potential and caveats of the various strategies, increase scientific and clinical interest in the field, and provide a forum for networking.

At the same time, a Norwegian Cancer Genomics Consortium (NCGC) was established by a group of cancer biologists and clinicians across the country. This consortium is a dynamic association of research groups who use tumor sequencing to investigate markers of therapeutic response, new therapeutic strategies, and basic mechanistic understanding that can be exploited in repurposing therapeutic strategies for new patient groups. The NCGC has successfully acquired two major grants from the Norwegian Research Council to establish 'A national research and innovation platform for personalized cancer medicine' (http://cancergenomics.no). The platform and projects are flexible, and will adapt to new technological developments and biological questions. An important objective has been to establish common routines and standards, so that results can be accumulated and compared across the country. Together with the Norwegian Cancer Registry, a pilot cancer genomics registry will be established to understand the issues of accumulating such data to analyze at a more epidemiological level. Major advantages include the presence of this national cancer registry, a common public health provider, personal ID numbers that enable tracking of clinical data throughout the health service, and a population that support public health research.

It is the hope that this platform will facilitate industrial collaborations, with regard to both clinical trials and target development. The consortium has a work package for the latter, to validate the functional impacts of patient-derived mutations in histotype-specific model systems, with a focus on kinases.

The first effort was centered around nine cancer types, with a project each on melanoma, colorectal cancer, leukemia, lymphoma, myeloma, breast cancer, sarcoma, prostate, and gynecological cancer. Given that the project does not have resources to compete with other large-scale sequencing efforts, it has focused on the strengths in the different clinical groups and the important questions that can be answered by sequencing the exomes of a limited number of patients, generally around 100 tumor-normal pairs. For some projects, samples have been investigated from clinical trials with different focuses, including therapeutic response, progression samples, tumor heterogeneity and clonal evolution.

Sequencing platforms have been set up, and a secure and encrypted storage and computing system established to protect the germ-line data. Approved users have signed a detailed contract including a guarantee not to re-identify patients, and by a two-point authentication process can log in from all partner institutions.

From their involvement with the International Cancer Genomics Consortium (ICGC), the NCGC team has experienced the complexities of mutation calling in cancer samples, and has participated in the current benchmarking study [6]. Although investigating full genome sequences at moderate coverage, this study demonstrated how the choice of apparently equivalent analytic tools, and the parameters used, gives highly variable conclusions from identical data. Although exome data are less complex, and tumor sequencing is carried out at an average depth of 300×, the issues leading to variable interpretation, such as normal stroma, subclonal heterogeneity, and areas of poor coverage, still apply. Thus, consensus procedures are needed from a national health service perspective. However, the variable combinations of mutational mechanisms in different tumors will require more fine-tuning before the large-scale methods are mature.

For sarcomas, a rare cancer, but more frequent in children and adolescents, the NCGC has, with funding from the Norwegian Cancer Society, been able to extend the NCGC-based study to a population-based, prospective study involving the sarcoma centers in all health regions in Norway (http://NoSarC.org). Although funding for thorough analysis is still incomplete, all sarcomas in Norway are being collected for 2–3 years, and their complete exomes sequenced. With further funding, expression profiling by RNA sequencing and high-resolution array comparative genomic hybridization (CGH) will also be done. RNA is generally important to be able to filter out mutated alleles that are not expressed; however, in sarcomas, RNA is particularly relevant for the discovery of fusion transcripts that are not the result of translocations revealed by routine diagnostics. Direct tumor grafts have also been established in immunodeficient mice, and *in vitro* cell lines have been derived from these, which will be excellent preclinical models to use to investigate patient-specific targets.

For orphan cancers, an important objective is to identify therapeutic targets for which drugs are already available but approved only for other cancer types. The efficacy of those drugs will then be further evaluated in the tumor grafts or other relevant preclinical models, and promising drugs proposed for small-scale trials (10–20 patients) that could indicate good expectations for Phase II trials. The NCGC team is also working on a national reporting system, by which the Cancer Registry could accumulate biomarker and outcome data for the many single-patient 'trials' that might be performed. This would enable the accumulation of experiences to guide further use. Such databases should preferably be international, and a commendable initiative has already been taken by the American Society of Clinical Oncology (ASCO; http://www.asco.org/practice-research/targeted-agent-and-profiling-utilization-registry-study).

However, although experimental treatments might be found that could offer new opportunities for small patient groups with no other options, the current focus on large randomized trials as the base for clinical practice and reimbursement makes clinical implementation challenging. Together with oncologists at the Kinghorn Cancer Institute in Sydney, the NCGC team is working on a 'Framework Protocol' (D.M. Thomas *et al.*, unpublished 2015), which uses a simplified format only seeking a likely response in a group of 10–15 patients with a candidate profile; in case of a promising result, this format is intended to lead to a larger, international study. To accrue a sufficient number of small groups of patients, extended international collaboration is important. With so many targets, and many more possible combinations, and only a few patients in each treatment group, extended networks of quality-assured trial organizations, as well as close public–private partnership for drug provision, will be needed to bring these new strategies and treatments to national health services in a sustainable way.

Given that there will never be sufficient resources in a public health system, the testing of new strategies will compete with available and expensive treatments with documented effect. Thus, separate funding and resources for routine treatment and academic trials or experimental treatments are needed. Otherwise, smaller patient groups and new nonproven strategies will always suffer. Furthermore, it is mandatory that physician time and supporting resources are available for such exploratory work. Without involvement in innovative projects, public health services will not be able to critically judge and apply the market-driven

development of the cancer treatment field, and will appear as lagging relative to the private health sector where patients can purchase the treatments and therapies that they want. This may erode the public support of the national health services.

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