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Current Perspective

Mainstreaming informed consent for genomic sequencing: A call for action

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Abstract The wider availability of genomic sequencing, notably gene panels, in cancer care allows for personalised medicine or the tailoring of clinical management to the genetic characteristics of tumours. While the primary aim of mainstream genomic sequencing of cancer patients is therapy-focussed, genomic testing may yield three types of results beyond the answer to the clinical question: suspected germline mutations, variants of uncertain significance (VUS), and unsolicited findings pertaining to other conditions. Ideally, patients should be prepared beforehand for the clinical and psychosocial consequences of such findings, for themselves and for their family members, and be given the opportunity to autonomously decide whether or not to receive such unsolicited genomic information. When genomic tests are mainstreamed into cancer care, so should accompanying informed consent practices. This paper outlines what mainstream oncologists may learn from the ethical tradition of informed consent for genomic sequencing, as developed within clinical genetics. It argues that mainstream informed consent practices should focus on preparing patients for three types of unsolicited outcomes, briefly and effectively. Also, it argues that when the chance of unsolicited findings is very low, opt-out options need not be actively offered. The use of a layered approach – integrated in information systems – should render informed consent feasible

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for non-geneticist clinicians in mainstream settings. (Inter) national guidelines for mainstreaming informed consent for genomic sequencing must be developed.

1. Mainstreaming informed consent for genomic sequencing

Genomic sequencing is becoming standard practice for selected patients with oncological conditions, including colorectal cancer, breast cancer, and ovarian cancer [1,2]. Often, genomic information is sought to improve diagnosis and prognosis and to guide the clinical management of cancer patients. Patients with aberrations in a BRCA-gene in ovarian tumours, for instance, may qualify for treatment with PARP-inhibitors [2]. Genomic sequencing has traditionally been offered through clinical geneticists or genetic counsellors working in specialised clinical genetics centres. Today, in many European countries, oncologists are increasingly ordering genomic tests directly, without involving clinical geneticists. This is referred to as 'mainstreaming' (see Box 1). As a result of more widespread use of genomic sequencing, especially gene panels (see Box 2), patients are increasingly confronted with intended and unintended genomic test results.

Genomic sequencing can yield three types of results that make them stand out from other clinical tests, namely: potential germline mutations, variants of uncertain significance (VUS) and unsolicited findings pertaining to other conditions. Germline mutations are genetic abnormalities that have been present in a patient since conception and thus reside in every cell of the patient's body, including their tumour cells. Some mutations, such as mutations in the BRCA1 and BRCA2 genes [2], when found in tumour cells, are known to likely be present in the germline, as well. Follow-up testing of other cells (e.g. blood cells) is usually required for confirmation. Germline mutations predispose patients to develop cancer. They also increase the likelihood that malignancies may strike again and prompt the need for risk-reducing interventions to avoid other cancer in the future. For a patient who has recently been diagnosed with cancer, learning about the presence of a germline mutation may have serious psychological and social, and potentially also socio-economic and clinical consequences. Moreover, as the mutation is present in the germline, the concurrent risk of cancer is heritable and may be – or may have already been – passed on to the patient's offspring, as well as shared by his or her parents and siblings. This means that testing of family members, so-called 'cascade testing', may be advised. Learning about a germline mutation can thus have serious implications for patients' family members, too.

VUS are variants that have not (yet) been associated with the disease, of which it is (as yet) unknown whether they are benign or pathogenic. In theory, for instance, there are tens of thousands of variants possible in the BRCA1 and BRCA2 genes. Although many of these have been detected in families or patients diagnosed with cancer, many others may have never been seen before and have not been reported before. If a hitherto unknown genetic aberration is detected on a virtual gene panel, it may be unclear whether or not it is associated with the patient's condition, and thus, it is (for now) classified as a VUS. For patients, learning about a VUS can be distressing [5], especially since VUS are usually not acted upon in clinical management. It is still a topic of discussion whether or not (or what types of) VUS should be reported to patients [6].

Genomic tests may also reveal unsolicited findings pertaining to conditions other than the oncological condition for which the patient is seeking help. Unsolicited findings are often characterised by their being beyond the aim of the test and by their relevance to the health of the patient. They are 'surprise findings that reveal unsuspected diagnoses or predispositions' [7] that

Box 1. Mainstreaming genomic sequencing.

Mainstreaming has been defined as 'the implementation of genetic/genomic testing in other specialities, for example, oncology, to aid diagnosis and/or treatment' [3]. For clinicians, it involves taking on new responsibilities. Before, medical oncologists or surgeons would triage cancer patients and refer eligible patients to clinical genetics centres, where they received pre-test and post-test counselling and provided informed consent for genomic sequencing. Now, medical oncologists and surgeons are increasingly ordering genomic tests themselves. In some versions of mainstream genomic testing pathways in oncology, the results are routinely disclosed and explained by a clinical geneticist or genetic counsellor [3]. In other versions, results are disclosed by the cancer team face-to-face or through a letter, and (only) those in whom potential germline mutations, variants of uncertain significance (VUS), or unsolicited findings have been detected are referred to a clinical geneticist or genetic counsellor [2]. These patients then receive counselling on the personal, clinical and reproductive implications of the test result and on the consequences for family members.

Box 2. Gene panels.

Recent developments in genomic sequencing technologies allow for rapid, reliable and increasingly affordable testing of multiple genes simultaneously. Some laboratories perform whole-genome sequencing and analyse the sequential order of all approximately three billion base pairs. Most, however, perform whole-exome sequencing, and analyse the sequential order of only those sections of DNA scattered across the genome that contain genes. Thus, the exome is the sum total of sections of DNA that are expressed or translated into proteins – about 1–2% of the whole genome. The analysis of whole-genome or exome data is often limited by the clinical indication; it is usually targeted at a subset of genetic variants that are known to be associated with the condition in question through the use of so-called 'virtual gene panels'. Gene panels for breast or ovarian cancer, for instance, will include known genetic variants in the BRCA1 and BRCA2 genes that are relevant to patient management, as they may affect the choice of treatment and eligibility for clinical trials or risk-reducing strategies, such as enhanced breast surveillance or prophylactic surgery [2]. The use of gene panels containing mostly clinically validated variants or variants known to be associated with the disorder in question thus facilitates the interpretation of genomic data and minimises the odds of detecting unsolicited findings. However, variants of uncertain significance (VUS) [4] may still be detected. Gene panels are available for oncological conditions but also for cardiological and neurological conditions [4]. While for oncological conditions, genomic sequencing is (initially) conducted on tumour cells (only), this is different for cardiological and neurological conditions. For these indications, genomic sequencing is conducted on blood cells that may immediately reveal germline mutations.

may be heritable and, again, have serious consequences, also for family members.

Depending on the strategy of analysis, findings pertaining to other conditions are rare. Estimates range from around 3% in research studies in which secondary findings are actively sought [8], to approximately 1% in open exome analyses and less than 0.1% in restricted disease-gene panels in experienced clinical laboratories (H.G. IJntema, personal communication). By contrast, germline mutations and VUS associated with the cancer in question are detected rather frequently. Germline mutations are found in about 15% of ovarian cancer patients [2] and in many childhood cancers [9]. Up to 40% of patients diagnosed with rare neuroendocrine tumours, such as paraganglioma and pheochromocytoma, are estimated to carry germline mutations [10]. VUS are no less frequent [11]. Thus, genomic tests may uncover findings beyond the clinical question in a significant number of cancer patients undergoing clinical genomic sequencing. Finding such variants is a routine part of genomic sequencing, also in oncology.

It is ethically and legally required that patients undergoing genomic sequencing are informed about 'the purpose and the nature of the test, as well as the implications of its results' [12], including unintended results, as part of the informed consent process. There are no data on whether this happens in cancer care, but observers are worried [13]. Information about genomic sequencing and its possible consequences is technically and biologically complex and may be difficult for clinicians to render [14]. Patients who are newly confronted with a cancer diagnosis may be emotionally troubled and unable or unwilling to consider genomic testing [15]. When patients fail to understand the implications of the test beforehand, they are more likely to experience distress afterwards [5]. How can this be improved?

Oncologists can look to the long-standing ethical tradition of pre-test counselling within clinical genetics, with its focus on dialogue, education and informed decision-making. Counselling is 'the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease' [16]. Traditionally, genetic counselling has been non-directive, and respectful of patients' autonomy. Clinical geneticists will inform patients, help them decide, and stress the so-called 'right not to know'. In clinical genetics, various new models for informed consent have been developed to facilitate informed consent for genomic sequencing, in general, and decision-making about the feedback of unsolicited findings in particular. Positive experiences were reported with a tiered (or differentiated) approach to informed consent, for instance, using four categories or 'bins' of unsolicited findings (ranging from actionable unsolicited findings to unsolicited findings of unknown significance (VUS)), from which patients were invited to choose [17,18].

Notably, layered consent may be helpful in mainstream settings (see Box 3). In a layered model, key information (the first layer) is discussed with every patient as part of the informed consent process, whereas additional, more detailed information is made available upon request. There is currently no guidance on what the first layer comprises – on what constitutes essential information or 'key information elements' [19] – for genomic sequencing in personalised medicine [14]. We argue that when patients undergo genomic sequencing as part of their cancer care, they should know – at a minimum – that doing so may entail learning about a suspected germline mutation, or, less likely, VUS or other unsolicited findings, which may be hereditary, and for which they may need to be referred to a clinical geneticist for follow-up. Oncologists should be able to explain this in general terms to cancer patients. Upon referral, patients can be informed more in detail by the clinical geneticist. But in mainstream settings, we

Box 3. Layered consent.

Oncologists may use a layered model for informed consent [19]. In layered approaches, the information that is provided as part of the informed consent process is subdivided into layers. In the first layer, essential or 'material' information is conveyed – key information that all (reasonable) patients need in order to provide informed consent. Since the early 1970s, this has commonly been referred to as the 'reasonable person' standard of disclosure. In the second, third and further layers, additional, more detailed information can be provided if the patient wishes to receive such information. People differ in their informational needs [21]. The layering of information helps to tailor the information provided to individual patients' informational needs, and thus, allows for 'personalisation' of informed consent. This is referred to as the subjective standard of disclosure [22]. Some people *need* more information than others in order to provide informed consent. To meet the subjective standard, dialogue (e.g. in the form of pre-test counselling) is indispensable.

propose, the first layer comprises (only) three key elements: all patients should understand that – in addition to the answer to the clinical question – genomic sequencing may bring to light potential germline mutations, VUS (when these are reported) and unsolicited findings pertaining to other conditions.

When using technical means (i.e. targeted analyses), unsolicited findings pertaining to other conditions can be largely avoided (e.g. reduced to less than 0.1%), clinicians who use this approach do not need to discuss the implications of such findings in detail with all patients, or actively offer an opportunity to opt out of feedback on unsolicited findings (in the first layer). When the chances are so slim, routinely inviting all patients to consider various categories of possible unsolicited findings may be disproportionally stressful and burdensome.

Box 4. Essential information and examples of brief explanations of the implications.

Germline mutations	'This means that your cancer may be hereditary. Knowing this may have consequences for you and for your family members'.
VUS	'Today, we do not know what such a finding means, but we may learn more in the future, and we may contact you again once we know more'.
Incidental findings	'There is a small chance that we find genetic risks for conditions other than your current condition. You may not wish to learn this information'.

A layered approach does entail, however, that during the informed consent dialogue, the oncologist should assess individual patients' informational needs and provide additional oral information when needed (see Box 3). Also, it may be useful to offer patients written information materials or help them find educational websites or decision tools [20]. Of course, patients can be referred to clinical geneticists for more information. Clinicians may need to give patients time to consider and process additional information about genomic sequencing. It should remain possible for patients to opt out of learning about germline mutations (associated with the cancer), VUS or other unsolicited findings.

While some mainstream specialists feel confident to take on counselling and informed consent for sequencing, others feel that they lack the time, capacity and expertise to adequately counsel patients [3]. We contend that clinicians need not be concerned. Oncologists are not expected to 'be able to interpret the technical details of the [genomic test] report' [13]. During consultations, they need not expound on the technical or biological details of genomics and sequencing technologies [15], on various categories of unsolicited findings, or on supporting patients with decision-making. Rather, they should focus on getting across the first layer of information, i.e. on helping patients prepare for possible outcomes and implications [23], which may otherwise catch them off-guard – by briefly pointing these out (see Box 4), which can be done relatively easily by oncologists with basic knowledge of genomics. When, during informed consent dialogues, clinicians note that patients have additional informational needs, they should be able to address these, for instance, by directing patients to suitable public information sources about genomic sequencing. For oncologists who are unfamiliar with genomics, additional professional genomics education and information sources may need to be made available [24,25]. Also, it should be noted that clinicians should adequately record informed consent in electronic patient records (including information provided, questions discussed (or not yet discussed) and consent provided) so that this can be shared with all stakeholders involved in the analysis of genomic data, notably with laboratory staff who prepare the lab report, so that the latter know, for instance, whether or not to include VUS or unsolicited findings.

In sum, we propose setting a realistic bar for informed consent practices for genomic testing for the purposes of personalised medicine in oncology settings – when appropriate. When gene panels are used, and the likelihood of unsolicited findings is very slim, the option to opt out need not be discussed in the first layer with all patients. First and foremost, clinicians should focus on helping patients understand – briefly, without too much technical detail – that potential germline mutations, VUS and unsolicited findings pertaining to other conditions may be uncovered – findings

that patients may not otherwise expect and which may have a major impact on them and on their family members. This way, patients are not hampered in autonomous decision-making by information overload, while they do receive sufficient information to make the decision to initiate genomic sequencing. (Inter) national guidelines for mainstreaming informed consent for genomic sequencing must be developed.

Author statement

Eline Bunnik: Conceptualization, Writing - Original draft preparation. **Wybo Dondorp**: Conceptualization, Writing – Reviewing and Editing. **Annelien Bredenoord**: Writing – Reviewing and Editing. **Guido de Wert**: Writing – Reviewing and Editing. **Martina Cornel**: Conceptualization, Writing – Reviewing and Editing.

Conflict of interest statement

None declared.

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