Author’s response to reviews

Title: Value-based genomic screening: Exploring genomic screening for chronic diseases using triple value principles

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Author’s response to reviews:

Dr. Maria Zalm
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Dear Dr. Maria Zalm,

We would like to thank you for inviting us to perform a major revision of the manuscript. Furthermore, we would like to thank both reviewers for taking their time and for providing useful advice on improving the content of the manuscript. As required, we are sending you the ‘change tracked’ version of the revised manuscript. Also, this document contains all of the queries raised by the reviewers. In our response, the paragraphs written by the reviewer start with RW#, and our answer to each comment starts with AU#.
Regarding to the comments of Dr. Wylie G. Burke our responses are the following:

RW1: How should allocative and technical values be applied to the use of screening based on exome or genome sequencing? The difficulty here is that the evidence base for clinical utility is highly variable for different genes.

RW2: What genes should be included if screening is accomplished in this fashion? How should this be decided? Perhaps the authors see the values principles as providing answers to these questions. if so, it would be helpful to discuss these issues explicitly.

RW3: For example - how would a values-based approach evaluate the ACMG recommendation for opportunistic screening of 59 genes when exomes are done? Would the technical evaluation be done separately for each gene, or should policy makers ask for outcome evidence on the use of the 59-gene panel? How does this choice affect allocative judgements? Without this kind of specificity, it is difficult to see how the values would guide decision-making.

RW4: As a corollary to the first point, it would seem that a major question for genomic screening is whether it is acceptable to censor some genomic information when massive parallel sequencing is used. Is it OK to screen for the ACMG list of 59 genes and deliberately choose not to report on non-actionable genes, such as early-onset Alzheimer Disease? If such censoring is appropriate, who decides what information is reported and what information is not reported? How would the three values assist in such decision-making?

RW5: Finally, the authors omit discussion of the potential for a major conflict between the allocative and technical values on the one hand and personal values on the other hand. The current literature suggests that many people appreciate the opportunity to have exome- or genome-based screening - with reporting not only of the ACMG list of 59 genes but also other genomic risk information, including polygenic risk profiles. Yet the evidence for all these forms of genomic screening is very limited. How should clinicians and policy makers respond if allocative and technical analyses argue against the use of exome-based screening (or any other form of genomic screening), while patient surveys demonstrate a strong preference for such screening?

AU1-5: 

We thank the reviewer for pointing out this relevant development in genomic sequencing and for raising the question how the value principles would be helpful in decision making. We think it is indeed important that we clarify our position on this development in the paper.
We now make it more clear in the Background/Current usage of genomic screening for chronic diseases sections that this article focuses on monogenic subforms of chronic disorders (such as familial hypercholesterolemia (FH) in cardiovascular disorders; BRCA and Lynch in cancer) given the substantial evidence base and proven cost effectiveness, that have resulted in clear guidelines for genetic testing of index cases and subsequent cascade screening of family members at risk. We use these case examples of deliberation on value in implementing genomic medicine in universal healthcare systems. Despite available guidelines, screening programs in many countries still have not been implemented.

Developments in sequencing technology and initiatives to implement opportunistic screening are relevant, but not the main focus of this paper therefore we would prefer to address the topical challenges raised by these developments separately in the Discussion section.

Sequencing is increasingly used to test the relevant genes also in the subforms we focus on, e.g. when sequencing and analysing a panel of genes implied in FH. Following the European Society of Human Genetics Recommendations, post-sequencing targeted analysis can be done focused on the gene or specific pathogenic and likely pathogenic variants in such a gene. Similarly, limited panels can be used, such as an onco panel in families where there is potentially an inherited tumor syndrome. Not necessarily all 59 genes as suggested by ACMG are considered for a deliberate search in European countries. National (multidisciplinary) societies and health authorities are implicated in decisions on which genes and gene variants to report as secondary findings on specific grounds. In universal healthcare systems, in particular, weighing evidence and pros and cons of selectively analysing and reporting secondary findings must be carried out to ensure optimal allocation of finite resources. We have addressed the issues raised in RW1 to RW5 in the text starting from line 308 (page 13) as follows:

‘In recent years, the introduction of Next Generation Sequencing (NGS) has generated a further complexity in weighing the pros and cons of genomic screening. The increased use of sequencing can improve diagnosis, however, the generation of Secondary Findings (SF) and Variants of Uncertain Significance (VUS) raises ethical, legal and social issues e.g. regarding consent and use of resources. For example, for cases where clinical sequencing is used, the American College of Medical Genetics (ACMG) has recommended a deliberate search for SF in 59 genes mostly unrelated to the health problem the patient presents with [50]. This might be regarded as opportunistic screening that optimizes the use of resources that have already been utilized but critical appraisals have pointed out that this approach runs counter to many standard premises in screening [51]. A major problem related to technical value is the variable evidence related to the different genes, especially regarding the penetrance and pathogenicity of variants in an unaffected population. In Europe, the European Society of Human Genetics (ESHG) has opted for a targeted approach [52]. After sequencing analysis can be targeted to the specific genes related to monogenic subforms of common disorders, such as FH, Lynch syndrome or...
BRCA-related breast cancer, similarly limited panels can be used, such as an onco panel in 

families where there is potentially an inherited tumor syndrome.

Professional societies and health authorities are currently implicated in decisions on which genes 

and gene variants to report as SF on specific grounds [53]. For instance, the French Society of 

Predictive and Personalized Medicine (SFMPP) elaborated guidelines for managing information 

on SFs for cancer related genes. „The main criteria were the ’actionability’ of the genes 

(available screening or prevention strategies), the risk evaluation (severity, penetrance, and age 

of disease onset), and the level of evidence from published data” [54]. The selected genes only 

partially overlapped with the ACMG oncology genes. While technical value focusing on the 

level of evidence is essential, prioritisation based on, for instance severity and penetrance, as 

well as on available resources for analysis, counselling and follow-up may inform national and 

local strategies to select specific subsets of genes in order to allocate resources proportionally. 

This typically is relevant in universal healthcare systems responsible for finite budgets. For 

instance in the UK’s 100 000 Genomes Project, a much more limited set of secondary findings 

has been selected in genes predisposing to bowel cancer, breast cancer and FH [55]. To assess 

allocative value, the resources devoted for people found to be a carrier of a mutation in SF 

without clinical symptoms would have to be evaluated. Resources spent on this group might be 

spent better in, for example, first degree relatives of BRCA1-carriers who are at 50% risk, while 

the population may be at &lt;1% risk. In some countries with universal health care systems, tests 

not subsidized by the healthcare service, can be available in the private sector so that tests with 

potential personal value to people are still available. Health authorities should make an effort to 

regulate appropriate information provision on the potential benefits and limitations of such 

testing to the public.’

Regarding to the comments of Dr. June C. Carroll our responses are the following:

RW1: The article appears to be written for a broad audience of what they call "healthcare 

professionals" including policy makers, payers and providers although some sections apply more 

to some than others. It might be helpful to be more specific in the conclusions regarding how 

each group might use the triple value principles in their work.

AU1: In the discussion we now specify that allocative value is primarily applicable for policy 

makers and payers, technical value is primarily applicable for providers and payers, and personal 

value is primarily applicable for clinicians within provider organisations. Also, we specified in 

some places which health care professional specifically has a certain responsibility, for instance 

at the beginning of page 7 – line 152: Every decision regarding the allocation of finite resources 

that policy makers and payers have to make has an opportunity cost.
RW2: I have some concerns about the term "genomic screening" - I think the authors should define this term. It seems to me that they use it to mean different things in their examples. Screening often implies "population screening" yet I don't think they mean this most of the time. They do however talk about implementing genomic screening "on a wide scale" which does somewhat imply that.

RW3: Sometimes they are referring to family history screening, sometimes cascade screening really unclear.

RW5: Line 71 - the authors say the paper is focusing on genomic screening of chronic diseases and that "the evidence base around using genomic screening for chronic conditions is relatively more established than its use for other conditions" - I'm not convinced that the paper is addressing genomic screening for chronic diseases - rather for relatively rare hereditary breast and ovarian cancer and colorectal cancer, and for more common familial hypercholesterolemia. Using family history as a screen might meet the criteria of screening for chronic diseases but I'm not sure the authors are always meaning that. These could be used as case examples for future implementation of genomic medicine but are not common chronic diseases. This relates to the definition of "genomic screening" and whether the authors mean population screening or not.

AU2, AU3 & AU5: We thank the reviewer for pointing out that our focus was not clear and have now specified in the Background that we do not focus on chronic disorders per se: ‘this paper will focus on genomic screening of some specific subforms of chronic diseases’ (page 3, line 71), and added that ‘the evidence base around using genomic screening for some monogenic subforms of chronic conditions is relatively more established than its use for other conditions [12]. More specifically the use of cascade screening after finding index cases has proven clinical utility.’ (page 4, lines 75-77).

In the beginning of the ‘Current usage’ section (page 4, lines 87-88) we have added that ‘Currently genomic screening (…) is implemented particularly in the case of monogenic subforms of some common chronic disorders…

In line 79 (page 4) we now better specify what we mean by genomic screening in this paper and what type of genomic screening we will focus on: ‘we use the term ‘genomics’, instead of ‘genetics’, to refer to screening for single and multiple genes because genomics is a broader term and techniques may range from single gene testing and genomic sequencing for analysis of single genes to techniques utilizing gene panels, such as oncopanels. The analysis presented in this manuscript is based on the targeted sequencing and/or analysis of the above-mentioned monogenic subsets.
In line 83 (page 4) we removed ‘the arguments presented do not differ when involving the screening of a single gene versus multiple genes’, as we felt this was not informative to our argument in this section.

In the section ‘Current usage’ section we now explicitly address that we focus on monogenic subforms and cascade screening rather than population screening as this is more (cost) effective.

Line 93 (page 4) now reads: ‘Rather than opting for population screening for these conditions, cascade screening of first degree family members of index cases proven to be (cost) effective for the aforementioned conditions.’

In addition, in line 96 (page 4) we added ‘Various strategies can be applied to identify index patients, including (combinations of) investigating clinical features and family history.’ We think this better prepares the reader for specific forms of case finding that are discussed in the examples in the section, thus avoiding confusion on the role of such case finding (e.g. family history) as first step in a broader screening program.

In line 98 (page 4) we added: ‘While several definitions of “screening” exist, in the context of this paper we focus on (i) systematic programmatic approaches (ii) the benefit of healthy persons.’

To further avoid confusion by using the general term genomic screening to be implemented on a ‘wide scale’ we have adapted line 122-123 (page 5) as follows: ‘However, despite progress in the field of genomic screening for chronic disease, such genomic screening programs with established evidence bases combining case finding and cascade screening are not implemented on a wide scale.’

RW4: The authors use the term "waste" - I think that should be defined in this context of genomic medicine.

AU4: At page 7 lines 158-160 we now included the definition: “spending on services that lack evidence of producing better health outcomes compared to less-expensive alternatives; inefficiencies in the provision of health care goods and services; and costs incurred while treating avoidable medical injuries, such as preventable infections in hospitals.” Followed by an example for genomic medicine (page 7, lines 162-170):
‘In the context of genomic screening, one category of interventions which have questionable benefit and could be deemed as wasteful are direct to consumer personal genome testing. As highlighted by McGuire and Burke: “Similar to other screening tests-or procedures of questionable clinical value that have been marketed direct-to-consumer, such as whole body CT scans, ordering follow-up tests and providing treatment on the basis of direct-to-consumer personal genome tests of indeterminate clinical value constitutes a raid on the medical commons [32].” It is the responsibility of policy makers, payers and providers to intervene when interventions like this put a burden on already limited resources and also pose a threat by potentially undermining the validity of genomic screening as a category of intervention in the minds of patients who are sometimes misled and given false hopes about what they can achieve.’

RW6: Line 88 - now they are talking about "screening of first degree family members" - ? of those with a known mutation - again more detail re definitions of what they are referring to would be helpful.

AU6: By integrating this sentence in the first paragraph of this section (rather than the beginning of a new section) and adding some detail we have tried to better explain that cascade screening of first degree family members is a central part of the genomic screening that we focus on in this paper. Line 93 (page 4, previously line 88) now reads: ‘Rather than opting for population screening for these conditions, cascade screening of first degree family members of index cases proven to be (cost) effective for the aforementioned conditions and is, therefore, recommended by prominent international bodies.’

RW7: Line 92 - "recommends screening all newly diagnosed cases for LS" - are the authors referring to testing first degree relatives of those newly diagnosed with LS - should be more specific - if so - agree this is cascade screening - not regular screening.

& RW8: Re LS - many countries are implementing routine/reflex testing of colorectal cancers for tumor markers suggestive of LS, then offering LS genetic testing to those individuals who test positive - sometimes I thought the authors were referring to this - but not clear.

AU7 & AU8: We thank the reviewer for pointing out this more adequate wording. We have changed the text as follows, in line 100 at page 5 ‘(EGAPP)…recommends to routinely investigate tumor tissue of all newly diagnosed CRC cases for markers suggestive of Lynch syndrome. Genetic testing can be offered to confirm diagnosis and reduce morbidity and mortality in relatives….’
RW9: Line 97 - I would suggest that women with positive screening results should "be offered" genetic counseling and if indicated - "offered" genetic testing.

AU9: We appreciate this suggestion for more precise language and line 109 (page 5) now reads: ‘Women with positive screening results are offered genetic counseling and, if indicated, offered breast cancer susceptibility genes (BRCA) testing...’

RW10: Line 99,100 - A "similar" program - is not clear - on reading reference 16 - both Georgia and Italy introduced a systematic collection of family history to indicate those who would be eligible to go on to genetic counselling - the author implies BRCA testing as a routine. Many countries use family history as a triage to identify those at increased risk of hereditary cancer - perhaps this is the "genomic screening" they are referring to (e.g. Eisen et al Genetic assessment wait time indicators in the High risk Ontario Breast screening program Molecular Genetics and Genomic Medicine 2017)

AU10: This has been rephrased as Programs of this kind were implemented in various countries, such as Georgia, Italy (Emilia-Romagna Region) and Canada (Ontario), and the suggested reference was added (page 5, lines 111-114).

RW11: Line 102 - Familial hypercholesterolemia - this is an example of cascade screening - seems to be mixing up family history identifying those at increased risk and cascade screening - they are quite different.

AU11: We think that by restructuring the first paragraph of the section Current usage (see also AU6) it is now more clear that FH is one of three examples that differ in the way index cases are found (e.g. via family history) after which a DNA test can confirm diagnosis and screening of family members can be started. To emphasize these different steps, we have added a sentence in line 115 (page 5) as follows:

‘In FH finding index cases may be based on clinical symptoms combined with systematically surveying family history after which a DNA test can confirm diagnosis.’
RW12: Line 103 - I don't understand the point of this Dutch example - needs better explanation.

AU12: We have shortened the information on the Dutch example to harmonise it with the examples mentioned on HBOC and Lynch syndrome. The fact that this was an official national screening program made it unique. Line 118 (page 5, was line 103) now reads: ‘The most famous example of such a cascade screening program existed in the Netherlands, where a national government subsidized program was active between 1994 and 2014.’

RW13: Line 133-135 - this concept of opportunity cost is true in all of medicine - might consider citing McGuire and Burke. An unwelcome side of direct-to-consumer personal genome testing: raiding the medical commons - JAMA 2008 - as they describe it eloquently.

AU13: The paper written by McGuire and Burke was useful indeed. We would like to thank you for making this suggestion! When defining waste in the context of genomics (at page 7, lines 162-167) we quote from their work and use their arguments.

RW14: Line 140 on - Resource allocation - this concept of disease areas having their own budget is complex and requires more discussion and justification - ref 29 could be elaborated on.

AU14: To avoid confusion and to make this section more harmonious with the central focus of the manuscript, we decided to remove the unnecessary explanation of program budgeting and rather focus on the benefits of moving away from silos to the disease burden within a population as the main measure to allocate resources (see page 8, lines 174-184).

RW15: Line 161 - Lynch syndrome associated with increased incidence of these cancers - at a younger age of onset generally.

AU15: The original statement was indeed unintentionally misleading. We have altered the sentence according to your suggestion (see page 8, line 195).
RW16: Lines 165-170 - yes - increased detection possibly earlier - this isn't a full cost/benefit analysis - more tests earlier vs sicker people later and death.

AU16: Our original intention was to inform the reader that the entire patient pathway needs to be considered when calculating the entire cost of a genomic screening. To clarify the message, we have added the aforementioned notion at pages 8-9, lines 199-201.

RW17: Lines 181 on - there are many reviews of these frameworks to evaluate genetic tests - one example is found at https://www.ncbi.nlm.nih.gov/books/NBK425803/ as there are more than cited here.

AU17: We thank the reviewer for the suggestion. We added the suggested reference to the manuscript (Technical value of genomic screening; page 9, line 213) and rephrased as follows:

‘The question of what factors determine the value of genomic applications has been debated for a long time and according to recent literature reviews, the ACCE framework and modified versions of HTA and the Wilson and Jungner screening criteria are the most common methods used by the scientific community to address this question [33, 34]. While the ACCE framework was developed specifically for the evaluation of genetic tests, the other approaches were developed to cover health technologies in general and then adapted or successfully applied to the evaluation of genomic technologies.’

Moreover, we briefly addressed some of the frameworks described in the suggested report i.e. EGAPP, USPSTF method and McMaster University framework, rephrasing as follows:

‘The ACCE model has been adopted and adapted by various entities since its development, both in the United States and worldwide. A substantial step in the ACCE’s evolution came in 2004, when the EGAPP (Evaluation of Genomic Applications in Practice and Prevention) initiative began to leveraged the ACCE model structure and experience and developed an initiative that supported the systematic assessment of genetic tests using the ACCE criteria as well as making recommendations for their use in clinical and public health practice [38].’ (Technical value of genomic screening; page 10, lines 234-240).
‘An example of HTA applied to the evaluation of genomic technologies is the framework developed by McMaster University to guide public coverage of new predictive genetic tests in Ontario [41]. The U.S. Preventive Services Task Force instead, uses the same HTA methodology developed for preventive services (i.e. screening, counselling, and preventive medications) for evaluating genomic tests also [42].’ (Technical value of genomic screening; page 10, lines 246-250)

RW18: Lines 218-223 - this is a good section on patient experience.

AU18: Thank you for this comment. The eight principles are very comprehensive and can be used in all areas of healthcare. This is the reason we included these in our arguments.

RW19: Line 232 - some reference on shared decision making would be good here.

AU19: Based on the suggestion, at line 285 (page 12) we cited the paper “Promoting Triple Value Healthcare in Countries with Universal Healthcare” as this was the first publication to discuss the three elements of personal value. We also cited the paper “Value Based Care and Patient-Centered Care: Divergent or Complementary?” as this promotes similar arguments with a different perspective.

We hope that these changes and responses are adequate for you and for both reviewers.

Sincerely,

The authors of the manuscript