16/09/2016

Submission of comments on 'Guideline on good pharmacogenomic practice' (EMA/CHMP/268544/2016)

Comments from:

Name of organisation or individual
Cancer Research UK

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Cancer Research UK is the world's largest independent cancer charity dedicated to saving lives through research. It supports research into all aspects of cancer and this is achieved through the work of over 4,000 scientists, doctors and nurses. In 2015/16, we spent £432 million on research in institutes, hospitals and universities across the UK. We receive no funding from the Government for our research and are dependent on fundraising with the public. Cancer Research UK wants to accelerate progress so that three in four people survive their cancer for 10 years or more by 2034. While guidance on good genomic practice is welcomed, the current draft guideline attempts to cover such a wide range of topics that its ability to provide definitive guidance on most of these is restricted. At the heart of the guidance is the consideration of quality in genomic analyses in general but the document focusses a disproportionate amount of attention on CYP genes and the effects of polymorphisms in drug metabolising enzymes throughout. It is unclear why this is the case and we would suggest drawing examples from a broader pool.	

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	There is a welcome discussion of a range of very distinct topics, including genetic polymorphism, the cancer genome, patient stratification, epigenetics, immunogenomics and drug labelling, but these discussions are relatively brief. While the bulk of the text in the document is a discussion of analytical quality, the default example is that of drug metabolising enzymes and the additional topics are relegated to descriptive statements that offer little or no guidance. This approach detracts from the central message in the guidance relating to the quality of pharmacogenomic analyses and therefore misses an opportunity for a more informative discussion of many of the very pertinent additional topics that are raised within. The document also focuses predominantly on examples of bad practice. A guideline should give equal attention to examples of good practice in order to promote learning. Suggestions:- • The document should be refocused to more clearly discuss the quality of genomic analyses in general. • If an extensive discussion of the genomic analysis of drug metabolising enzyme polymorphism is required, it could be collected into an appendix to this guidance or covered in a separate guidance.	

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	• Examples are frequently used in isolation. Where examples are used these should be to explicitly underline specific principles and should illustrate a range of challenges in genomic analysis rather than concentrating solely on those that relate to drug metabolising enzymes. • Consideration of the quality and challenges of genomic analyses should clearly differentiate germ line genome analyses from that of somatic mutations, such as cancer. The challenges of these two areas are so distinct that covering the two simultaneously in one document is not informative to either. • Topics such as the use of genomics for patient selection, immunogenomics, the heterogeneity and plasticity of the tumour genome, the future of personalised medicine and the dynamics of drug labels could be separated into appendices or (preferably) a separate guideline on personalised medicine. • Given the document provides examples of genomic biomarkers used in patient selection, a more in depth discussion of the impact of personalised medicine on drug labelling would be welcome.	
	We are interested to know who is on the working group.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
67-70		Comment: This sections states that circulating DNA is not covered and then states that the main focus is genomic DNA (circulating DNA includes genomic DNA). Lines 249-255 then describe using liquid biopsies for circulating tumour DNA. Proposed change: The guidance needs to be decisive about the scope of inclusion and communicate this more clearly and consistently.	
132-167		Comment: The principle pitfalls are all listed first and all the examples follow later – this makes it difficult to interpret which example relates to which pitfall. Proposed change: Each bullet (lines 132-140) should be followed by an example. Each example should explicitly relate to the bullet. Examples of good practice should also be used.	
144-159		Comment: A number of examples of bad practice are provided, including an alarming case where somatic DNA was analysed instead of germline DNA. Were these examples of bad practice published and what was the outcome? Which organisations produced the research? No reference is provided. Proposed change: Examples should be referenced. Unreferenced examples have much lower impact.	

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168-187		Comment: The examples given suggest input came from a very specific field of expertise. Proposed change: Suggest seeking broader input on areas such as this in order to capture the full picture.	
245-248		Comment: This section would benefit from inclusion of a positive example e.g. where a drug focused on a single genetic mutation *can* be effective across multiple cancer types Proposed change: An example of a scientifically sound 'basket study' (such as the National Lung Matrix trial) should be included.	
264-271		Comment: It is unclear whether circulating tumour DNA can be used to detect epigenetic modifications. The first and second paragraphs appear contradictory on this issue. Proposed change: the guidance should be clear on the use of circulating tumour DNA.	
290-299		Comment: Whole genome sequencing (WGS) and whole exome sequencing (WES) do create large quantities of data. However, if data handling is a major burden then it should be noted that targeted diagnostic testing produces significantly less data and should be used whenever appropriate. Proposed change: The guidance should be clearer about when WGS and WES techniques are appropriate.	

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312-313		Proposed change: Procedures should be recommended for withdrawal of consent.	
361-363		Comment: Increasing the number of reads to solve challenges associated with high GC content is particularly resource intensive. Proposed change: The guidance should include other techniques such as decreased fixation time, optimisation of DNA extraction, utilising alternative analysis algorithms.	
520		Comment: Suggest alternative use of phrasing rather than 'Profit' Proposed change: 'Benefit' would be more appropriate.	

Cancer Research UK anticipates that the use of molecular diagnostic testing will play a key role in the future of cancer clinical trials and access to precision medicine, and we welcome the opportunity to respond to this consultation. We spend £30-40m per year directly on precision medicine, supporting 11 large stratified trials as well as funding other large programmes and infrastructure. We are increasingly moving towards a model where cancer patient treatment decisions are made on an individual basis at the initiation of treatment, monitoring response, and at the point of recurrence.

Molecular diagnostic tests present an opportunity to radically improve our ability to tailor treatments to individuals. As more targeted therapies become available, there will be an increasing need for clinicians to routinely perform diagnostic testing and interpret complex data sets – and to do all this in a way that can benefit therapeutic choices in real-time. We therefore welcome the opportunity to comment on this guidance.

For further information, please contact Ed Blandford, Policy Adviser, via Edward.blandford@cancer.org.uk or 0203 469 6122.