

Response to GTR Request for Comments

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1. No, all tests should be included in the GTR.
2. The major use of the GTR will be to locate tests. It also may allow comparisons between labs and tests which currently is difficult. The biggest roadblock is that most users will need education in how to use the information.
3. The data elements listed in #6 are critical for all users. Most will only check a, c, and j. It will be important to raise awareness and encourage them to pay attention to the other data elements.
4. Benefits and risks
 - a. Public and clinicians without training in genetics may misinterpret information and order test inappropriately.
 - b. Most genetic tests will have limited information on clinical validity. It would be easy for this to discourage the use of a test that could be beneficial. It is important that benefits and risks be discussed and that will be difficult to do with the registry. It will be important to distinguish between a positive result and a “true” negative.
 - c. Same as b.
5. There is a difference between “unknown” and “not reported”. Most genetic tests will have several blanks in the “unknown” category. GTR needs to provide some discussion on how to use the information.
6. Data Elements
 - a. Contact – YES, also note if the lab has a genetic counselor and if the lab will talk with patients
 - b. Certifications – YES, also include professional guidelines that lab strives to follow – ACMG, AMP, CAP – most government oversight is at a “minimal level” and there needs to be a way to recognize the labs that are working at a higher standard.
 - c. Name – YES – but should have to give all names that might be used
 - d. Regulatory clearances – YES, but currently this will not exist for most genetic tests. Some insurers have used the lack of this to deny testing inappropriately. Will be important to explain this in a way that it does not increase this problem.
 - e. Intended Use – YES – information will be different based on intended use. This will make GTR harder to develop.

- f. Recommended patient population – YES – but who is going to decide? – probably better to include populations that have been tested and those that have not. GTR should consider stronger statements - “test may not be reliable in other populations”.
- g. Limitations – YES – every test has limitations – need to make sure users realize that.
- h. Test methodology – YES – methods are not standard and not interchangeable. GTR should provide a description of each method – targeted sequencing, gene sequencing, gene sequencing with intronic boundaries, etc. Labs should then be required to list where they differ from the description. Labs will not automatically include all details and by providing a reference description this may increase the ability to compare tests between labs.
- i. Analyte – YES – this is a major problem for genetic testing – what is the analyte – one common mutation, a panel of mutations, all exons, all exons plus intronic boundaries, multiple genes, etc. - GTR should develop category descriptions and provide educational materials
- j. Specimen requirements – YES - also what to collect in and how to submit
- k. Availability – GTR will have to maintain this because it is a moving target – also need to be clear on not using research testing for clinical care – it is illegal to release non-CLIA results
- l. Accessibility – YES – also include information to take to health care provider
- m. Performance characteristics – YES – this information will be difficult to provide and will be a moving target – most likely based on research and validation process and it will be inaccurate – clinicians may use a test as a “rule-out” which could give it a low value incorrectly. Might be more important to ask “how does the test compare to the existing technology or clinician diagnosis”. Performance characteristics depend on what is the analyte – you can have high sensitivity for a single mutation yet low for all mutations – in a quick comparison clinicians and patients may not understand. Important to distinguish difference in a positive result and a negative result – performance values will be different. Important for lab to explain proficiency testing – see 6b
- n. Clinical Validity – this category should be used with caution – it has been verified for almost no genetic tests and could be read as a negative when it is actually a lack of information and a lack of funding to collect information – also how does it compare to the other testing options – is a clinician diagnosis more likely to give the answer (often not).
- o. Utility – NO – there is no data for this on almost all genetic tests – a lack of this information could easily be misused – instead consider “impact on diagnostic pathway”
- p. Cost – NO – labs discount and hospitals mark up tests, so this will provide little relevant information

7. Clinical validity and utility will be almost impossible to provide. Even if provided it will probably be based on research which looks at a very selective population and probably does not apply in the real world.
8. Developing a system to allow comparisons among tests and labs would be important. Many clinicians do not understand the limitations of many tests. As more testing is performed by primary care providers, it will be important to provide tools to determine the best test for each patient – “the patient specific test”.
9. References – YES, but there are very few of these.
10. GTR should provide as much educational material as possible. GTR should describe each testing technology and the benefits and limits of each. Labs can then comment on where they vary, but providing this information for every test will require a lot of work.
11. Time and the fact that this is not reimbursed. Also that it could easily be used to make a test look questionable, when clinicians are very comfortable with the test and can use it with its limits.
12. See that it is widely used. Labs will only contribute the information if it increases test volume.
13. ?
14. Consider using the CETT Program model of two diagnostic pathways to predict potential clinical utility. Labs must have some benefit in posting or they will not.