Practical Issues in Identifying and Communicating Incidental and Unexpected Findings Arising from Mutation Analysis Utilizing Next Generation Sequencing for Clinical Oncology.

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Abstract

Introduction: With the maturation of next generation sequencing platforms in clinical diagnostics the wealth of data that is generated in a time efficient and cost effective manner. One consequence of generating increased amounts of clinical data is the detection of incidental and/or unintended findings. A key consideration for many clinical labs is how to report or communicate these incidental findings to the ordering physician. Recently the ACMG has released a set of guidelines for reporting incidental findings; however, this article does not meet the needs of a genetics oncology laboratory on several fronts. Therefore, it is essential to identify and adopt a set of standards for reporting incidental findings detected in tumor samples that addresses the special needs of personalized medicine in oncology.

Methods: Mutation analysis was performed using the Truseq Amplicon Cancer Panel (Illumina) to determine the mutation status of select regions of 44 genes. Ordering physicians have the ability to order mutation analysis for single genes, a subset of 9 genes associated with therapy response or the full set of 44 genes for clinical trial associations. For all genes not reported, all mutation positive results are evaluated by a clinical geneticist to determine if the case merits further discussion. Mutations that have implications for clinical trials, potential germ line inheritance, therapeutic response to chemotherapy or diagnosis are flagged and discussed in a greater group comprised of geneticists, pathologist and literature scientists. In order to appropriately identify patients with potential germ line inheritance of a mutation we employed several criteria that included examining age at cancer diagnosis, allele frequency of the mutation and the gene that is mutated.

Results: In our analysis of over 5,000 samples that received mutation analysis by next generation sequencing ~75% of cases did not report results for all 44 genes. Of those cases we identified 17 eligible for clinical trial enrollment, 13 of potential germ line inheritance, 5 with a diagnostic dilemma, and 6 with FDA approved therapy implications. Two of the cases that posed a diagnostic dilemma resulted in a change of diagnosis following a consultation with the ordering physician and pathologist.

Conclusion: Establishing a standard procedure for dealing with incidental or unexpected findings in oncology will be necessary as more labs adopt next generation sequencing platforms. Using our current method of identifying incidental findings ~1% of cases are flagged for review making this procedure tenable for high throughput oncology labs.

**Please note this abstract has deviated from the original submission*

ACMG Guidelines[1]

1. Assume the ordering physician has a detailed understanding of genetics
2. Assume that the patient has had appropriate pre-test genetic counseling
3. A minimum list of genes should be examined for all whole exon or whole genome cases, laboratories can expand on this list
4. Report out mutations with known clinical impact
5. Report the incidental finding regardless of age
6. Add variants to existing report without first consulting physician
7. The ordering clinician will provide appropriate post-test genetic counseling

Criteria for Identifying Incidental Findings

General Criteria

- Mutation must be detected with >99% confidence
- Mutation cannot be a variant of unknown significance
- Test was not ordered by the treating physician

Clinical Trial and FDA approved Therapies

- Mutation would directly effect therapy response or may attenuate a therapy response
- Clinical trials available for mutated gene and tumor type

Diagnostic Dilemma

- Mutation and mutated gene must be well described in a different cancer
- Mutated gene not consistent with diagnosis

Potential Germ line Inheritance

- Patient must have a mutation in a gene associated with an inherited genetic disorder
- Mutation must be present >50% of tested alleles
- For cancer disposition syndromes, presence of cancer prior to age of 50 (Multiple sarcomas or cancer before age 40 for TP53)

Results

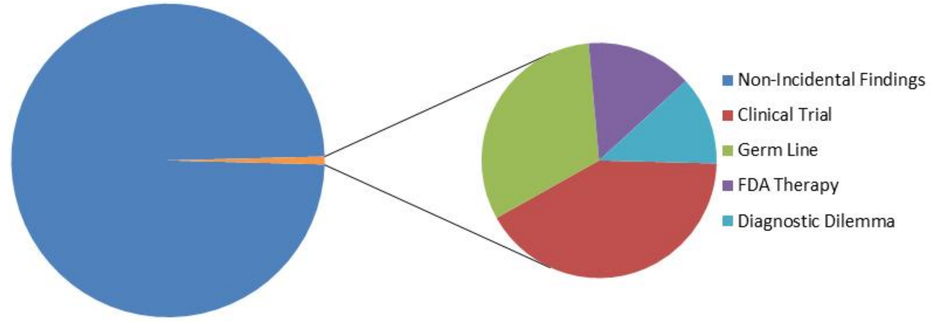

Figure 1 – (Left) A pie chart displaying the proportion of incidental findings a representation of all samples tested. (Right) A pie chart displaying the breakdown of the different incidental findings detected at Caris.

Incidental Finding Disclosure Procedure

1. Incidental finding identified by geneticist or pathologist
2. Incidental finding consensus committee alerted to finding. Consensus committee consists of at least:
   - Medical Director
   - Director of Genetics
   - Pathologist or Geneticist presenting finding
   - Literature Scientist
3. Consensus committee determines whether a phone call is needed utilizing, but limited to, the following criteria:
   - Tumor primary
   - Mutation
   - Gene mutated
   - Mutation frequency
   - Family history (if available)
   - Presence of multiple primary tumors
   - Clinical/pathological features
   - Literature review
4. If physician contact is needed either a pathologist or geneticist will call the physician to discuss the incidental finding and the importance
5. Physician will elect to give a verbal order to clinically report out the result. For some patients an Advance Beneficiary Notice (ABN) may be required to report out result
6. Report result if requested and document interaction

Conclusions

- Current ACMG guidelines are designed for laboratories performing genetic testing for inherited disorders, they do not adequately address the needs of laboratories specializing in oncology
- Four main incidental findings are detected in our laboratory and each needs district criteria for identification
- In the oncology setting it should be assumed that the ordering physician does not have intimate knowledge of genetics nor has the patient been appropriately counseled
- Our current policy yields an incidental finding rate of ~1%
- Disclosure of results may require the patient to sign an ABN prior to reporting of the incidental finding

References

1. Green, RC. et al., *ACMG Recommendations for Reporting Of Incidental Findings in Clinical Exome and Genome Sequencing.* Genetics in Medicine. 15:7, July 2013. 565-574