The Role of *In Vitro* Diagnostic Tests in Pediatric Master Protocol Development

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Anand Pathak, MD, PhD, MPH

Medical Officer

Molecular Genetics Branch

Division of Molecular Genetics and Pathology

Office of In Vitro Diagnostics and Radiological Health (OIR)

Center for Devices and Radiological Health (CDRH)

Disclaimer

No financial relationships to disclose

Thoughts on new regulatory issues and policies are preliminary and do not represent finalized FDA policy

Outline

- Role of *In Vitro* Diagnostics in Precision Medicine and Pediatric Master Protocols
- Regulation of Investigational Products
- Criteria for determination if a study is Significant Risk, requiring an Investigational Device Exemption.
- Example: Analytical validation requirements for an IDE of an NGS targeted oncopanel

Precision Medicine

- The success of Precision Medicine in Pediatric Master Protocols depends on having accurate, reproducible and clinically useful tests to identify patients who can benefit from targeted therapies

- "A bad test is as bad as a bad drug."

- Dramatic increase in biomarker-targeted drug development programs
  - In the early 1990s, 5% of new drug approvals were for targeted therapies
  - In 2013, 45% were for targeted therapies

In Vitro Diagnostic

Definition: Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body .

Source:

21 CFR 809.3

Therapeutic Products and In Vitro Diagnostic Devices for Precision Medicine

- Treatment is often targeted, and selection often relies on IVD test result
- Expectation that IVDs will inform best use of anti-tumor agents
- Targeted treatment often involves tumors that are uncommon, with respect to factors such as age, histology, and biomarker(s)
- **Same regulatory paradigm applicable to one biomarker is applicable to Pediatric Master Protocols with treatments directed to many different molecular variants for a range of histologies.**

IVD: Definition: Those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body . 21 CFR 809.3

Precision Medicine for Pediatric Cancers

- The type of tumors in the pediatric population are different from the adult population.
- There can be significant molecular heterogeneity within a single histology of cancer.*
- **With tools available for characterizing this heterogeneity, there are new opportunities to develop more effective, personalized treatments for pediatric cancers**. *
- Pediatric cancers have significantly lower mutational burden than do adult cancer, ranging from **0-18 protein coding alterations compared to a median of 44 non-silent mutations in adult cancers.** *

*Khan et. Al., JAMA Oncology May 2016 Volume 2, Number 5, p. 575-577

Precision Medicine for Pediatric Cancers:

EXAMPLE: Baylor College of Medicine Advancing Sequencing in Childhood Cancer Care Study*

- BASIC3 (WES, pediatric solid tumors): 121/150 had produced interpretable results. 4 (3.3%) had mutations of established clinical utility, 29 (24.0%) had mutations of potential utility and 24 (19.8%) had mutations in other consensus cancer genes.

- In the BASIC3 study: By germline examination, 15 (10.0%) of patients had pathogenic or likely pathogenic mutations.

***BASIC3:** Parsons DW, Roy A, Yang Y, et al. Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors [published online January 28, 2016]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.5699.

Khan et. Al., JAMA Oncology May 2016 Volume 2, Number 5, p. 575-577;

Precision Medicine for Pediatric Cancers:

EXAMPLE: Individualized Cancer Therapy (iCAT) Study*

- Originally used Targeted NGS -- Sequenom Oncomap: 471 mutations in 41 cancer related genes (initial assay)
- FFPE or frozen tissue, patients with brain tumors not included
- They switched to the OncoPanel with Agilent SureSelect for target capture and Illumina for sequencing – full exons of 275 cancer genes and 91 introns (in 30 target genes)
- Had aCGH for CNV and whole transcriptome sequencing on some samples.
- Tumor Profiling successful in 89 of 100 patients; technical failure in 11 patients.

*__iCAT Study:__ Harris MH, DuBois SG, Bender JLG, et al. Multicenter feasibility study of tumor molecular profiling to inform therapeutic decisions in advanced pediatric solid tumors: the Individualized Cancer Therapy (iCat) study [published online January 28, 2016]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.5689.

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Precision Medicine for Pediatric Cancers:

EXAMPLE: Individualized Cancer Therapy (iCAT) Study*

- Cancer-associated signaling pathway gene mutation (n=10) and CNV alteration in MYCN (n=6) and cell cycle genes (n=11)
- Therapeutic recommendations in 31 patients but only 3 received the targeted therapy.

Reasons for not receiving the suggested therapy were that the cancer was too advanced (3 [15.8%]), no active disease was present or the disease was well controlled with the patient's use of another therapy or the patient was already receiving third-line therapy (8 [42.1%]), clinical status was not appropriate for targeted therapy for unknown reasons (4 [21.1%]), and the patient could not access the appropriate investigational therapy (4 [21.1%]).

*__iCAT Study:__ Harris MH, DuBois SG, Bender JLG, et al. Multicenter feasibility study of tumor molecular profiling to inform therapeutic decisions in advanced pediatric solid tumors: the Individualized Cancer Therapy (iCat) study [published online January 28, 2016]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.5689.

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Precision Medicine for Pediatric Cancers*

- Sequencing of the both the **primary tumor and the relapsed tumor may be useful.**
- In the future, there may **be use of liquid biopsies** (e.g., cfDNA from plasma) to guide and monitor treatment in pediatric master protocols.
- **Sequencing has to be very rapid**, as the patient's disease can progress before the NGS assay results are available.
- There is also the possibility of the patient **developing resistance to the targeted therapy.**

*Khan et. Al., JAMA Oncology May 2016 Volume 2, Number 5, p. 575-577

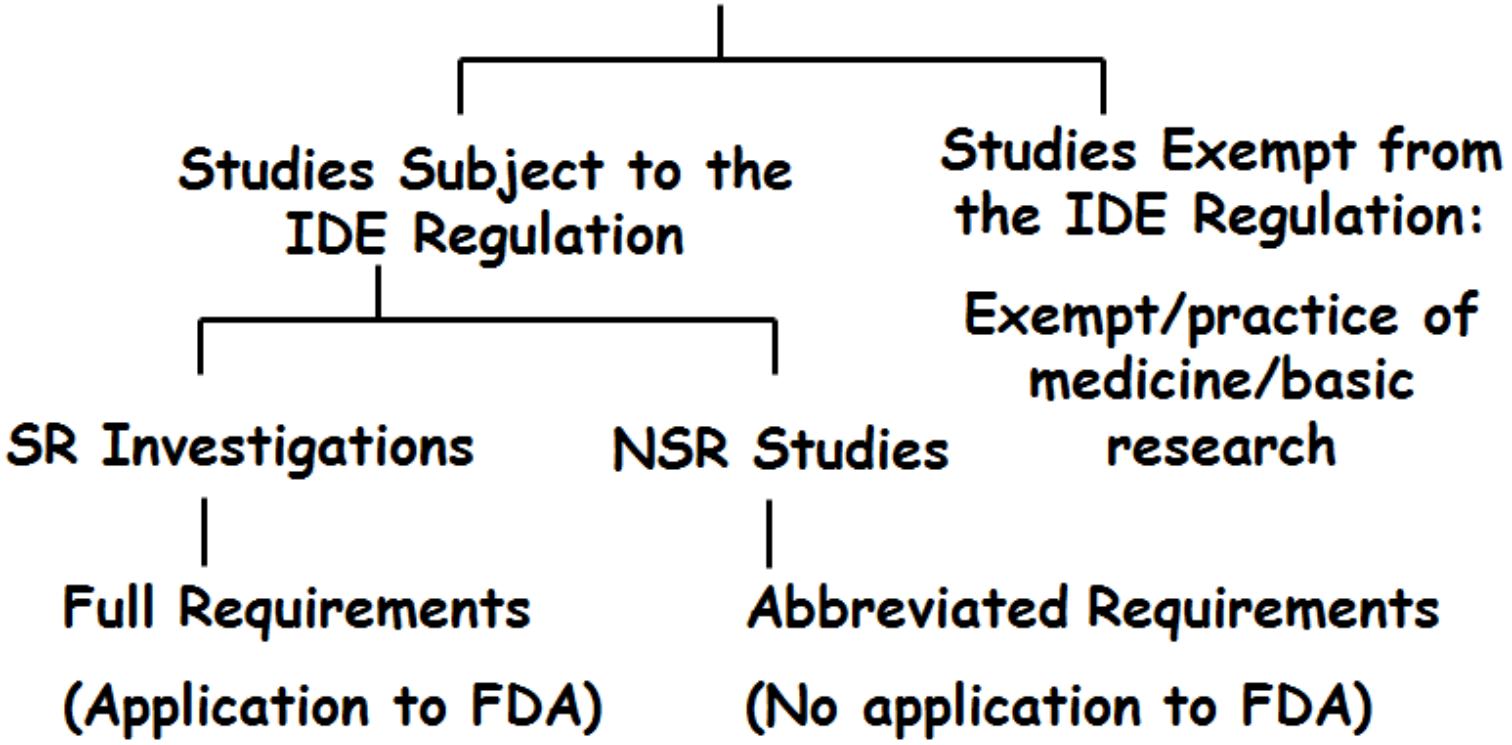
Device Example for Pediatric Master Protocol

- Targeted Next Generation Sequencing of a “hotspot” oncopanel (5000 hotspots)
- Covering SNV, indels, CNV and translocations
- The matrix of actionable mutations (at the variant level) and drugs are specified *a priori*
- **Possible scenarios:**
  - relapsed/refractory disease or primary cancer (are there effective/approved therapeutic alternatives?)
  - there may be a requirement for biopsy during investigation

Investigational Device Exemption (IDE)

– Investigational Device Exemption (IDE) – The purpose of the IDE regulation is **to encourage**, to the extent consistent with the protection of public health and safety and with ethical standards, **the discovery and development of useful devices intended for human use…** **CFR 812.1**

Investigational Device Exemptions (21 CFR 812)



For an SR study, an approved IDE is required; the NSR study has abbreviated requirements, but the device in such a study, should have analytical validation.

You can submit to FDA a risk-determination pre-submission to determine risk of an investigational device study.

CDRH purview includes the regulation of investigational in vitro diagnostic devices

- The sponsor and IRB can make a determination about exempt/NSR/SR status without resort to an SRD submission to CDRH
- A Risk Determination from CDRH evaluates the level of risk of the use of a specific device in a specific trial
- Potential benefit does **not** influence this determination
- **For investigational use of a Significant Risk device, FDA approval of an IDE application is required**

Risks with Investigational use of In Vitro Diagnostic (IVD) Devices

- KEY QUESTION: What are the potential harm of the use of the device in the trial.
  - Will misclassification of patients as false positive or false negative by the investigational test, lead to significant potential harms of the use of the device in the trial. Potential harms include forgoing alternative effective treatment.

Study Risk Determination Criteria For Companion Diagnostic Tests with an IND

1. Are patients going to be foregoing alternative effective therapeutic options?

2. Are patients going to be exposed to adverse events that are worse than the standard of care?

3. Is there any information that is known about the test result subsets that makes it worse for someone if the test result is wrong?
   - Is there prior knowledge that one of the biomarker subsets would fare worse on the Investigational drug than under standard of care?

4. Are there "significant risk" biopsies planned for the sole purpose of testing (serious morbidity or mortality can occur from the biopsy)?

Investigational Device Exemptions

IDE applications require:*

- The device must be clearly defined
- The device must undergo a minimum level of analytical validation
- Informed consent form includes certain information

*IDE regulation: 21 CFR 812 in sections 812.20 through 812.38

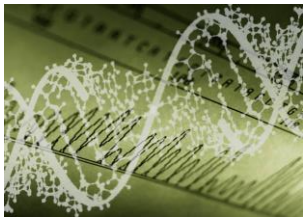
Purpose of IDE Review for Significant-Risk Devices

- Complete specification of the device, for purposes of the investigation
  - May be essential for interpretation of results from a therapeutic product's biomarker-driven clinical trial; i.e. **if you don't have a fully specified, analytically validated device to measure the biomarker, trial results will be difficult to interpret**

Current Thinking on NGS Oncopanels: Standardization of Pre-Analytical Protocols



- Pre-analytic: sample acquisition, laboratory processing, DNA purification, etc.
- It is strongly recommended that sponsors establish procedures that specify the process for pre-analytical sample processing parameters prior to the start of the trial.
- If the pre-analytical metrics and procedures are established and standardized, the data generated from the trial is more likely to be informative.



Current Thinking on Analytical Validation of NGS Oncopanels

- Assessment of accuracy, limit of detection, and precision/reproducibility of the NGS device for a *representative subsets of variants* covering different variant types, sizes and genomic regions, should be performed.
- Analytical accuracy should utilize *well-validated orthogonal methods*
- Assessment of representative tumors are recommended; should also include challenging tumor types.

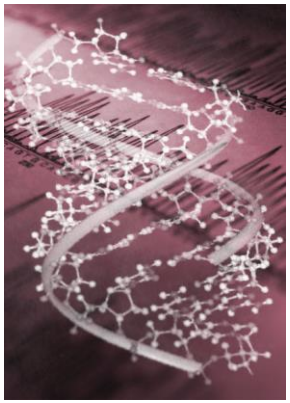
Changing Mutation Panels

- Mutation panels may be updated with new actionable mutations of interests and new therapeutic targets.
- Appropriate re-validation (in a “least burdensome way”) would be required upon such changes, to ensure analytical validity.

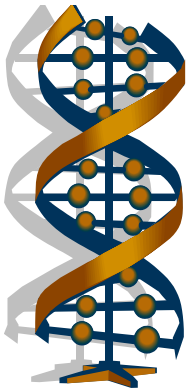
Germline Testing

- It may be useful to perform germline testing on patients as well to determine whether a mutation is hereditary or somatic.
- As many as 10% of pediatric cancer patients may have germline mutations (BASIC3 Trial).
- Thus, there may be utility in having tumor-normal pairs from sequencing.

Conclusions



*"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? " * -- President Obama, January 30, 2015*



- The success of Precision Medicine in Pediatric Master Protocols depends on having accurate, reproducible and clinically useful tests to identify patients who can benefit from targeted therapies
- IDE applications for investigational tests are intended to help assure that the performance of tests are reasonably reliable and assure interpretability of findings from these clinical trials.

https://www.whitehouse.gov/precision-medicine

References

BASIC3: Parsons DW, Roy A, Yang Y, et al. Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors [published online January 28, 2016]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.5699.

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Editorial: Khan J and Helman LJ. Precision Therapy for Pediatric Cancers. [published online January 28, 2016] *JAMA Oncol.* doi: 10.1001/jamaoncol.2015.5685

President Obama Quote: https://www.whitehouse.gov/precision-medicine

Abbreviated Requirements

CFR 812.2.C

Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981

Exempt Studies

CFR 812.2.C

Exempted investigations. This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.


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