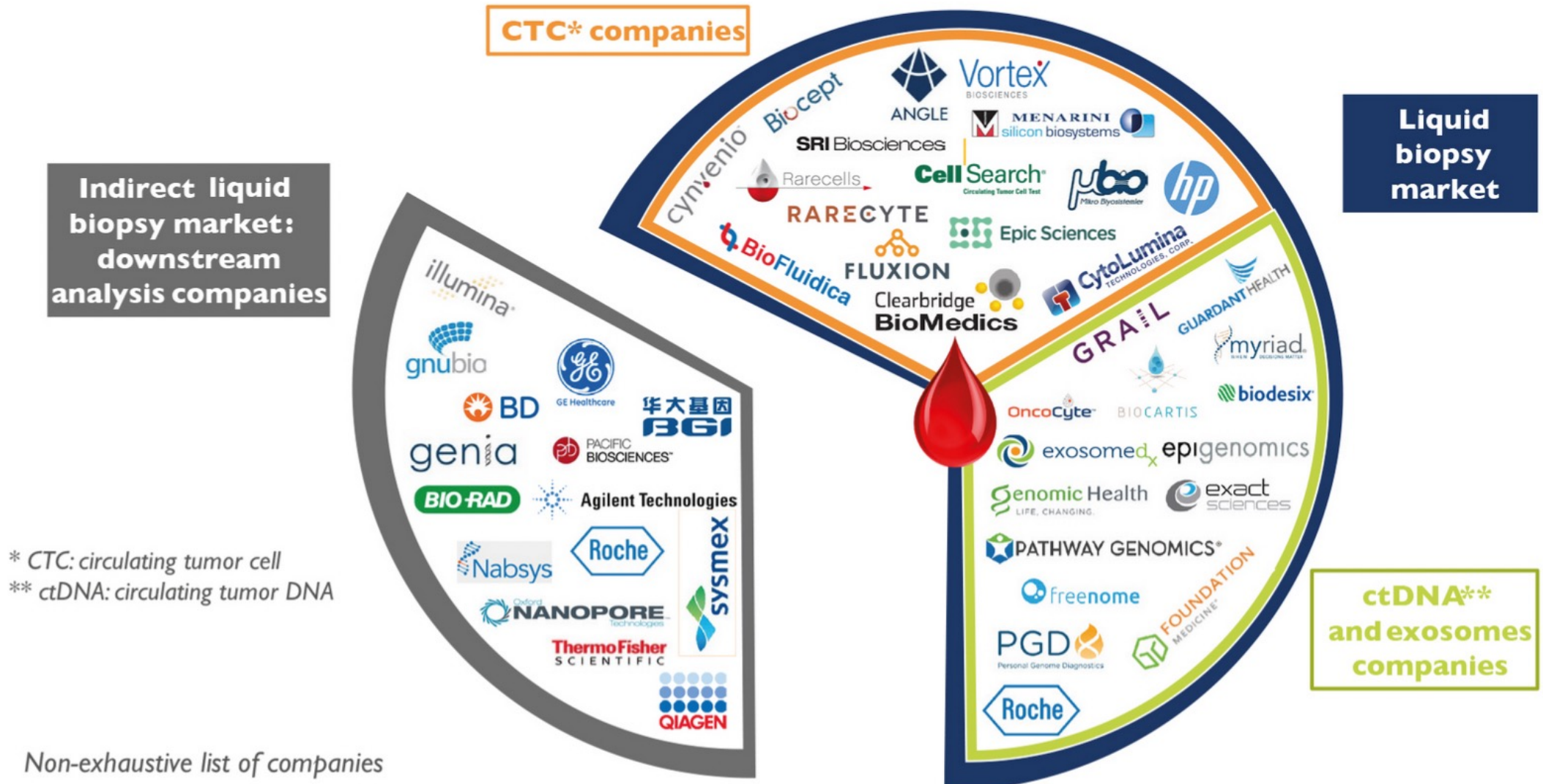
ctDNA
out of the Dark

Artwork by Lina Lennerz


CTC* companies
Liquid biopsy market
Indirect liquid biopsy market: downstream analysis companies
ctDNA** and exosomes companies
* CTC: circulating tumor cell
** ctDNA: circulating tumor DNA
Non-exhaustive list of companies
Vortex BIOSCIENCES
ANGLE
Biocept
cynvenio
MENARINI silicon biosystems
SRI Biosciences
Rarecells
CellSearch
RARECYTE
Epic Sciences
BioFluidica
FLUXION
Clearbridge BioMedics
CytoLumina TECHNOLOGIES, CORP.
illumina
gnubio
GE Healthcare
BD
华大基因 BGI
genia
PACIFIC BIOSCIENCES
BIO-RAD
Agilent Technologies
Nabsys
Roche
sysmex
NANOPORE
ThermoFisher SCIENTIFIC
QIAGEN
GRAIL
GUARDANT HEALTH
myriad
biodesix
OncoCyte
BIOCARTIS
exosomedx
epigenomics
Genomic Health
exact sciences
PATHWAY GENOMICS
freenome
FOUNDATION MEDICINE
PGD
Roche

FRIENDS of CANCER RESEARCH

ctMoniTR Project

ctDNA for Monitoring Treatment Project

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

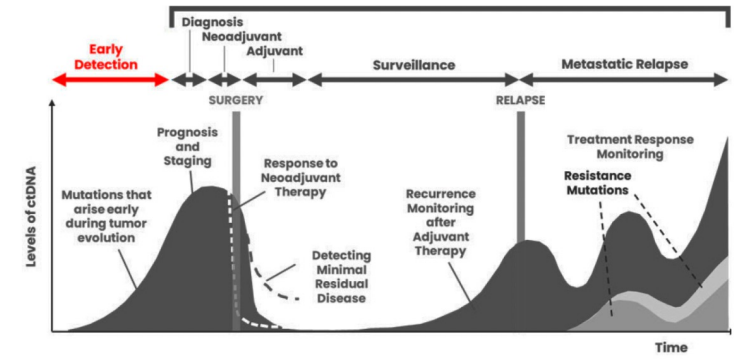
Assessing the Use of ctDNA as an Early Endpoint in Early-Stage Disease

Friends of Cancer Research Annual Meeting 2021

Introduction

Circulating tumor DNA (ctDNA) is a dynamic biomarker

Figure 1: Potential Use Cases of ctDNA in Oncology. Depicted is a time course through a patient's cancer treatment journey and the opportunities for use of ctDNA to guide treatment. (Adapted from Natera)



Friends of Cancer Research Virtual Meeting

Expediting Drug Development: Use of ctDNA as an Early Endpoint

Wednesday, July 20, 2022

11:30AM EDT - 1:00PM EDT

Agenda

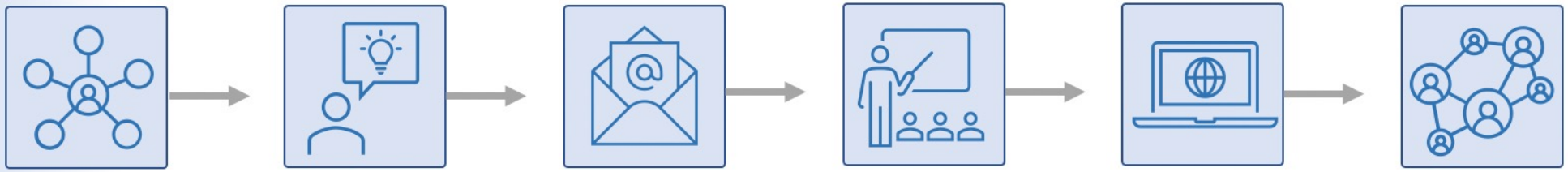
- Introduction PIcc
- Overview of the ctDNA Project
  - Review, inform, comment
- Overview of the Guidance
  - 5 sections
  - comments
- Discussion
- Consider Commenting
- Draft, review, submit (if applicable)

Pathology Innovation Collaborative Community

- Regulatory science initiative
- Facilitate Innovation
- Advance safety and effectiveness evaluations
- Harmonize approaches to speed delivery to patients
- Collaboration in the **pre-competitive space**
- Open to all stakeholders

Pathology Innovation Collaborative Community

The Alliance for Digital Pathology and AI/ML



You value Collaborations

You have a Regulatory Science Project

Focus is NOT on competitive product development

You propose your project to PIcc

You present to steering committee

PIcc helps organize the project

PIcc does NOT actively participate in your project

PIcc is a network to find interested collaborators

PIcc is a collaborative community that provides the infrastructure to connect stakeholders

Overview of the Project

Review

- Provide an opportunity to the network
- Provide a chance to discuss and talk to others

Inform

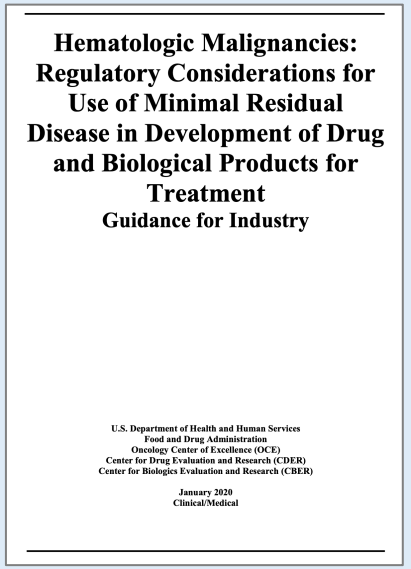
- Provide a web-based **resource** on the topic
- Enable networking and critical review of the draft guidance
- Consolidating shared experience of multiple stakeholders

Consider commenting

- Commenting period is still open
  - Consider providing feedback (positive and/or negative)

I. Introduction

- Distinguish ctDNA
- Scope: includes investigational new drug application (IND)
- Reference to: Guidance Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment (Jan. 2020)



Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2020
Clinical/Medical

resource….
https://www.fda.gov/regulatory-information/search-fda-guidance-documents

II. Background

- ctDNA as a biomarker has regulatory potential

  E.g., may assist and expedite drug development

- Emphasis on early-stage cancer setting
- Enrichment strategies
- Detecting MRD confers poor prognosis
  - Residual ctDNA = molecular residual disease
- ctDNA assessment vary among laboratories and technologies
- Need for further standardization

Early-stage

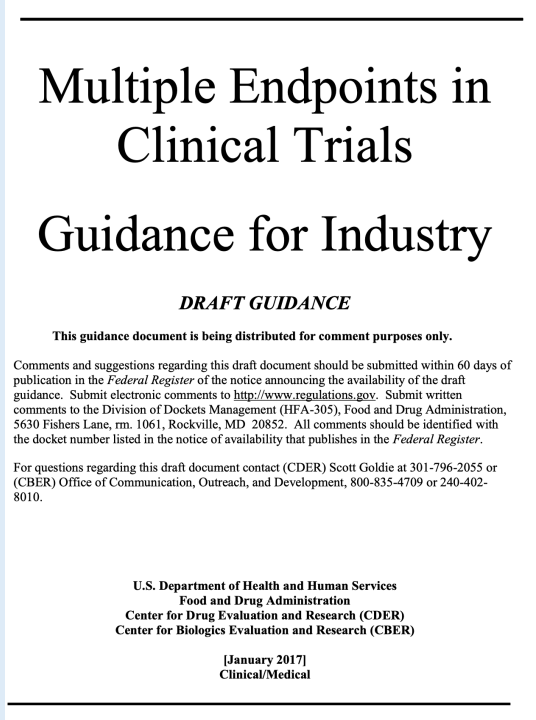
Contains Nonbinding Recommendations
Draft — Not for Implementation

II. BACKGROUND

Drug development for solid tumors in the early stage, non-metastatic setting, typically involves large trials and multiple years of conduct and follow-up with time-to-event endpoints. Certain patients with early-stage solid tumors can be cured with local therapy alone (e.g., surgery, radiation or chemoradiation), other patients require (neo)adjuvant systemic therapy in order to be cured, and others may progress to metastatic disease despite surgery and/or systemic therapy. ctDNA is tumor-derived fragmented DNA shed into a patient's bloodstream that is not associated with cells. ctDNA quantity can vary among individuals and depends on the type of tumor, location, stage, tumor burden, and response to therapy. ctDNA as a biomarker has a number of potential regulatory and clinical uses in the early stage setting that may assist and expedite drug development. In the early-stage cancer setting, ctDNA may be used to detect a certain targetable alteration, to enrich a high- or low-risk population for study in a trial, to reflect a patient's response to treatment, or potentially as an early marker of efficacy. We will discuss each of these potential uses below.

III. Development of ctDNA as a Biomarker for regulatory use in early-stage solid tumor clinical trials

- A. ctDNA for patient selection based on Molecular Alterations
- B. ctDNA Molecular Residual Disease for Patient Enrichment
- C. ctDNA as a Measure of Response
- D. ctDNA as an Early Endpoint in Clinical Trials



Multiple Endpoints in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

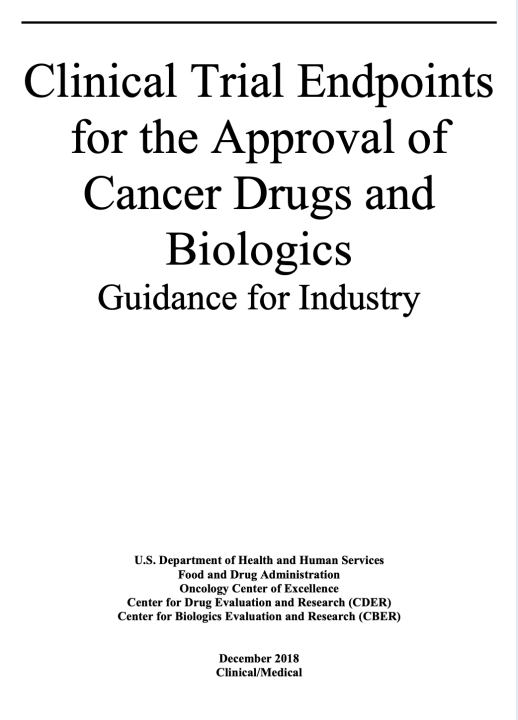
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Scott Goldie at 301-796-2055 or (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

[January 2017]
Clinical/Medical



Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2018
Clinical/Medical

ctDNA as a Measure of Response

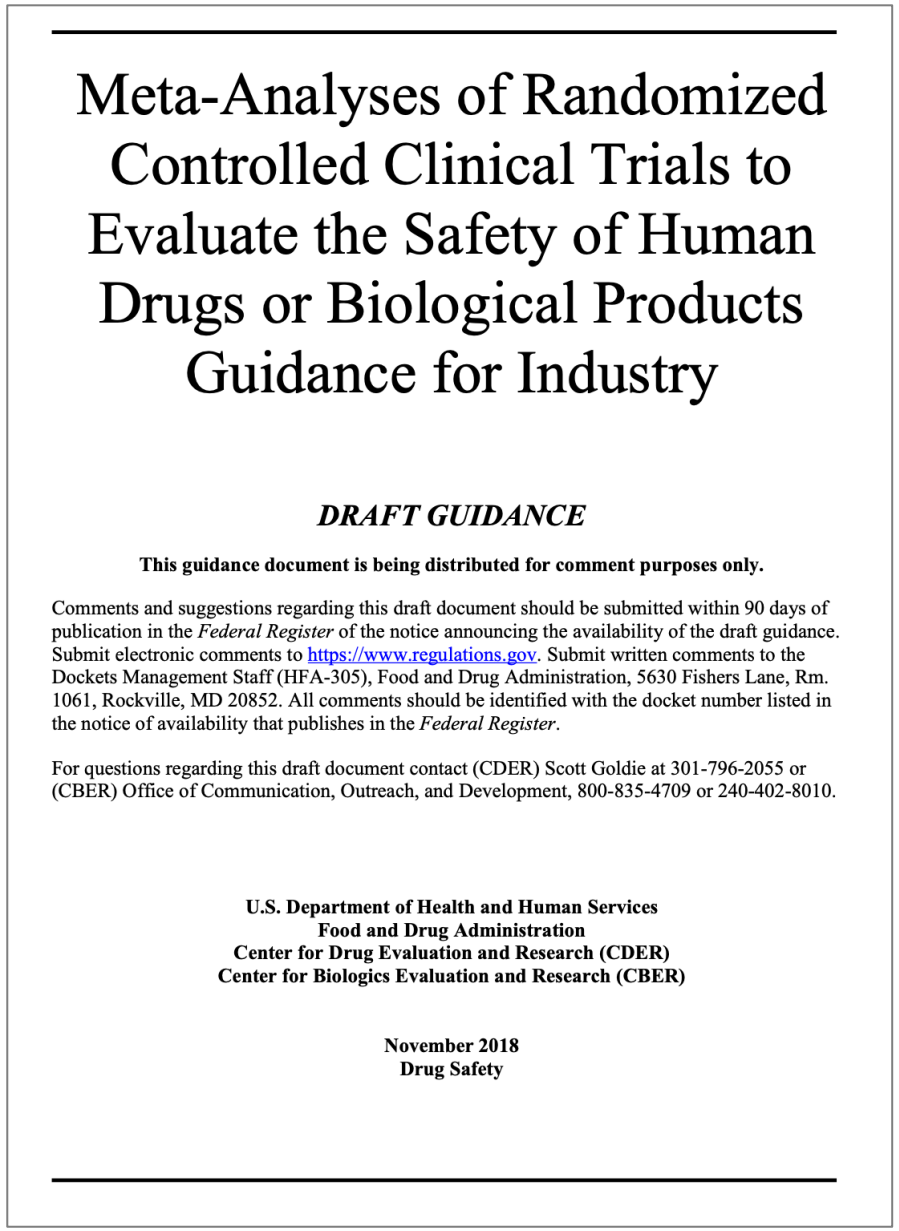
C. ctDNA as a Measure of Response

- ctDNA could be used in early phase clinical trials to aid in signal finding of drug activity and to potentially aid sponsors in their drug development plans.
- FDA encourages Sponsors to develop evidence regarding the usefulness of ctDNA response in addition to or supporting pathologic complete response information after neoadjuvant therapy.

ctDNA as an Early Endpoint in Clinical Trials

ctDNA as an Early Endpoint in Clinical Trials:
Although not currently validated for use, changes in ctDNA in response to a drug may have the potential to be used as an early endpoint to support drug approval in the early-stage cancer setting.

- Further data are required to support the use of ctDNA as an endpoint reasonably likely to predict long term outcome (DFS/EFS/OS).
- Trials that collect ctDNA data before and after drug treatment should also collect long term outcome data to characterize the association between ctDNA clearance and outcome.
- Various statistical criteria have been proposed for validating an endpoint and often meta-analytical approaches have been used. [6] An appropriate meta-analysis to validate ctDNA at a trial level association should include only randomized trials. Sponsors should discuss and provide details of any proposed meta-analysis plan to validate use of ctDNA in a particular context of use with the FDA.
    - The plan should include details of trial designs, inclusion and exclusion criteria, ctDNA assessment methods, and disease setting. A justification for the suitability of pooling the studies should be provided.
    - Trials should include a patient population representative of the population in which the endpoint ultimately will be used.
    - An adequate number of randomized trials with sufficient follow-up time should be included and justified.
    - Analysis based on individual patient-level data should allow an assessment of individual-level association.
    - Prespecified criteria for concluding association based on both trial-level and individual -level association measures, including prespecified timing and window of ctDNA assessment should be provided.
    - Long-term clinical endpoints, such as EFS/DFS and OS that have been clearly and consistently defined across studies should be included.
    - Sponsors should explore the effects of missing data on trial results.



Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Scott Goldie at 301-796-2055 or (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2018
Drug Safety

IV. Assay Considerations

- A. **Types** of Molecular Residual Disease Panels
- B. **Sampling** Considerations
- C. Assay **analytical validation** considerations for marketing applications

Types

- Tumor informed vs. naïve
  - Informed: Tu seq => then select variants
    - –lag time
    - Sensitivity/specificity depend on clinical cutoff and analytical sensitivity
  - Naïve: tumor agnostic
    - Marker not covered
    - Whole genome sequencing

A. Types of Molecular Residual Disease Panels

MRD panels can utilize tumor-informed methods, tumor-naïve methods, or a smaller panel of candidate genes each with its own strengths and limitations as summarized below:

- Tumor-informed panels are constructed by sequencing the tumor and then selecting a set of variants to follow.
  - Limitations of this approach include lag time between tumor testing and ctDNA panel creation, and sensitivity and specificity may depend on clinical cutoffs and analytical sensitivity of the device as well as the number of tumor informed targets assayed.
- Tumor-naïve or "tumor-agnostic" panels are those that are not informed by sequencing or by mutations of the primary tumor. This approach uses panel-based next generation Sequencing (NGS) to ascertain MRD.
  - Limitations include tumor markers not covered by the ctDNA panel and additional characterization of panels would be needed to understand what percentage of patients are trackable with such techniques.
  - Whole genome sequencing (WGS) could potentially be used in a tumor-naïve fashion. This would allow the use of other biomarkers besides mutations, epigenetic alterations (e.g. methylation) or fragmentomic analysis of ctDNA to capture tumor derived ctDNA signals.

Multiple markers on a candidate gene panel could help assure that the MRD assay will serve its function, even with the development of additional cytogenetic changes.

Sampling

- Shedding affected by histology, grade, stage size
  - Timing of ctDNA testing
- Set time point
- Multiple time points
  - Scientific rationale, pre-determined
- Time point same across study arms
- Baseline sample
- Study sides should follow similar protocols

Sampling Considerations

There are several sampling considerations related to the clinical trial design and the intended use patient population that should be taken into account.

- The shedding of ctDNA is affected by histology, grade, stage, and size of the tumor thus timing of ctDNA testing should be discussed with the FDA and should be supported by performance characteristics of the test, disease characteristics and tumor biology.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- A set time point should be chosen for enrollment into the study and pre-specified.
- If a sponsor wishes to use multiple ctDNA time points to determine eligibility (e.g. screening paradigm evaluating if intervention at early detection of recurrence would influence outcome) this should be supported by scientific data/rationale. Sensitivity analyses based on different time windows could be explored (but should be predetermined and discussed in advance).
- The timing of ctDNA testing should be the same across study arms.
- A baseline pre-treatment sample should be collected to allow for consideration of the impact of variation in tumor shedding rates on assay performance. In addition, this sample will allow for interpretation of the post-treatment sample for study enrollment.
- All sites in the study should follow standardized protocols for sample collection, storage, and processing and handling.

Analytical Validation

- Validation study
- Entire assay system (from tube to market ready assay)
- Validation approach can differ for tumor-naïve vs. informed types of assays
- Clinical samples + contrived samples
- Fixed panels: cell lines/spiked
- Personalized panels: cell lines representing number and types of variants should be developed
- Precision
- Reference materials

C. Assay analytical validation considerations for marketing applications

Analytical validation ensures that the assay measures the analyte or analytes that it is intended to measure in the intended tumor type. Analytical validation should be conducted to establish the performance characteristics of the assay. Validation studies should be acceptable in terms of the assay's sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol, which may include specimen collection, handling, and storage procedures.[7] The acceptance criteria for the validation studies should be adequately justified to support clinical use.

- MRD assay validation should encompass the entire assay system from sample collection (e.g., blood collection in the specific collection tube that will be used with the final market ready assay) to the output of the assay including the detection threshold (cut-off) that determines positive vs negative patients. The cutoff should be established appropriately (e.g., both in terms of allelic frequencies or mutant molecules of the variants per ml of plasma and number of variants that are required to be positive in personalized panels for MRD positivity).
- The assay cutoff should be established to optimize assay sensitivity and specificity for the clinical use. Analytical performance should be robust to detect MRD positivity accurately and reproducibly.
- The assay should have high sensitivity and negative predictive value (NPV) for supporting de-escalation of treatment and high specificity and positive predictive value (PPV) for supporting escalation of treatment.
- The validation approach of an MRD test will depend on the type of MRD testing modality. As noted in section IV A., there are different

ıary of Safety and Effectiveness Data (SSED) for the Guardant360 CDx PMA P200010: www.accessdata.fda.gov/cdrh_docs/pdf20/P200010B.pdf

Contains Nonbinding Recommendations
Draft — Not for Implementation

types of MRD testing approaches that are currently under development. For tumor-naïve NGS-based MRD panels, panel-based validation of fixed panel content will be needed; however, for tumor-informed NGS-based personalized panels, the panel content will vary for each patient and therefore the assay validation will be based on each personalized assay. The validation strategy to support the device marketing application should be discussed with CDRH/FDA.

- Samples from clinical trials (clinical specimens) are recommended to be used for key assay validation studies such as confirmation of the assay limit of detection (LoD), assay precision, analytical accuracy, assay input studies. In some analytical validation studies since a large volume of sample will be needed, clinical samples may be supplemented by contrived samples. In general, when using contrived samples in assay validation studies, the functional equivalency between the contrived and clinical samples should be demonstrated and rationale should be provided if contrived samples are used to substitute or supplement clinical samples in certain studies.
- For fixed panels, cell lines carrying the specific alterations (i.e., cell line DNA spiked into an appropriate matrix) may be used as contrived samples. For personalized assays, cell lines that represent a distribution of the number and type of variants based on early clinical study data should be developed.
- Assay precision should be demonstrated using samples across the detection range of the assay including samples at the assay cutoff and samples with the minimum analyte requirements.
- An appropriate set of reference materials should be developed to allow for comparability across multiple MRD assays.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Next Generation Sequencing Oncology Panel, Somatic or Germline Variant Detection System

Device Trade Name: Guardant360® CDx

Device Procode: PQP

Applicant's Name and Address: Guardant Health, Inc.
505 Penobscot Drive
Redwood City, CA 94063 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200010

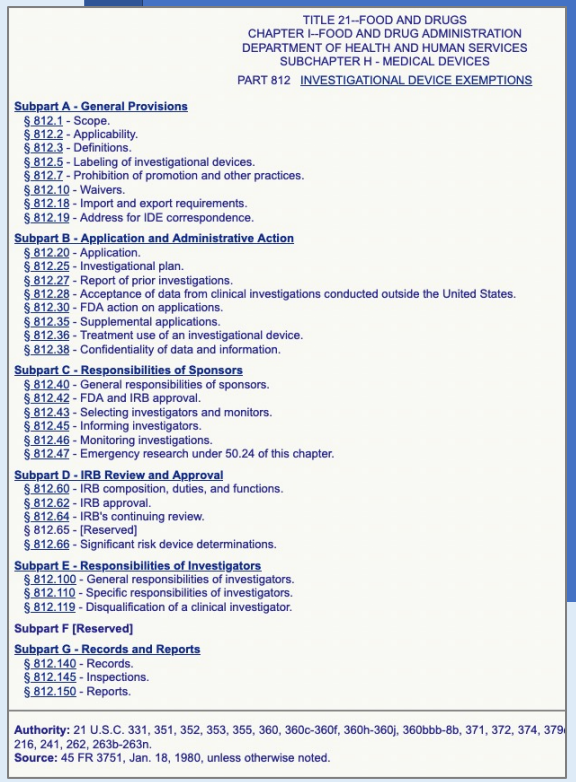
Date of FDA Notice of Approval:

Breakthrough Device: Granted breakthrough device status (formerly known as
Expedited Access Pathway, or EAP) on January 29, 2018 because the device (1)
intended to provide more effective diagnosis of a life threatening or irreversibly
debilitating disease or condition (2) represents a breakthrough technology that p
clinically meaningful advantage over existing legally marketed technology, and
availability of the device is in the best interest of patients.

A De Novo (DEN200001) for Streck Cell-Free DNA Blood Collection Tubes (E
was also submitted for the use of the Streck Cell-Free BCTs with the Guardant3
DEN200001 was authorized on August 7, 2020 in conjunction with the approva
P200010.

V. INVESTIGATIONAL DEVICE CONSIDERATIONS

- Subject to IDE
- Significant risk ⇔ non-significant risk ⇔ exempt
- Sponsor submits Study Risk Determination
- (optional streamlined submission process)



TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES

PART 812 INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A - General Provisions
§ 812.1 - Scope.
§ 812.2 - Applicability.
§ 812.3 - Definitions.
§ 812.5 - Labeling of investigational devices.
§ 812.7 - Prohibition of promotion and other practices.
§ 812.10 - Waivers.
§ 812.18 - Import and export requirements.
§ 812.19 - Address for IDE correspondence.

Subpart B - Application and Administrative Action
§ 812.20 - Application.
§ 812.25 - Investigational plan.
§ 812.27 - Report of prior investigations.
§ 812.28 - Acceptance of data from clinical investigations conducted outside the United States.
§ 812.30 - FDA action on applications.
§ 812.35 - Supplemental applications.
§ 812.36 - Treatment use of an investigational device.
§ 812.38 - Confidentiality of data and information.

Subpart C - Responsibilities of Sponsors
§ 812.40 - General responsibilities of sponsors.
§ 812.42 - FDA and IRB approval.
§ 812.43 - Selecting investigators and monitors.
§ 812.45 - Informing investigators.
§ 812.46 - Monitoring investigations.
§ 812.47 - Emergency research under 50.24 of this chapter.

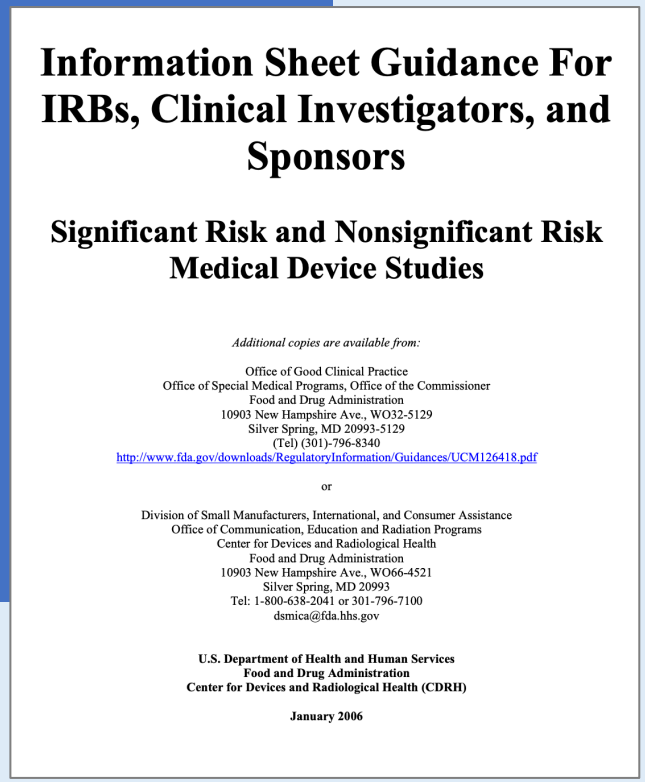
Subpart D - IRB Review and Approval
§ 812.60 - IRB composition, duties, and functions.
§ 812.62 - IRB approval.
§ 812.64 - IRB's continuing review.
§ 812.65 - [Reserved]
§ 812.66 - Significant risk device determinations.

Subpart E - Responsibilities of Investigators
§ 812.100 - General responsibilities of investigators.
§ 812.110 - Specific responsibilities of investigators.
§ 812.119 - Disqualification of a clinical investigator.

Subpart F [Reserved]

Subpart G - Records and Reports
§ 812.140 - Records.
§ 812.145 - Inspections.
§ 812.150 - Reports.

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 360bbb-8b, 371, 372, 374, 379
216, 241, 262, 263b-263n.
Source: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.



Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

Additional copies are available from:

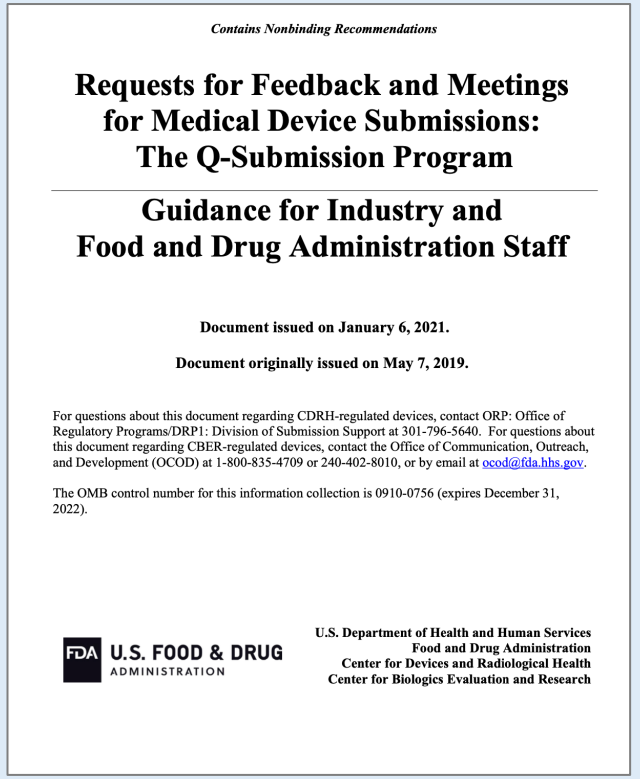
Office of Good Clinical Practice
Office of Special Medical Programs, Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., WO32-5129
Silver Spring, MD 20993-5129
(Tel) (301)-796-8340
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

or

Division of Small Manufacturers, International, and Consumer Assistance
Office of Communication, Education and Radiation Programs
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., WO66-4521
Silver Spring, MD 20993
Tel: 1-800-638-2041 or 301-796-7100
dsmica@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)

January 2006



Contains Nonbinding Recommendations

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on January 6, 2021.

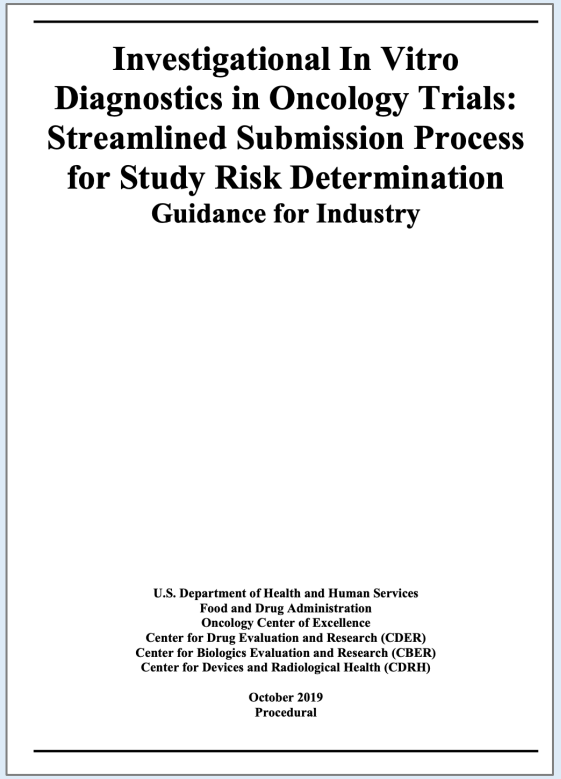
Document originally issued on May 7, 2019.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

The OMB control number for this information collection is 0910-0756 (expires December 31, 2022).

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research



Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

October 2019
Procedural

Discussion: Commenting

Notes

Next steps

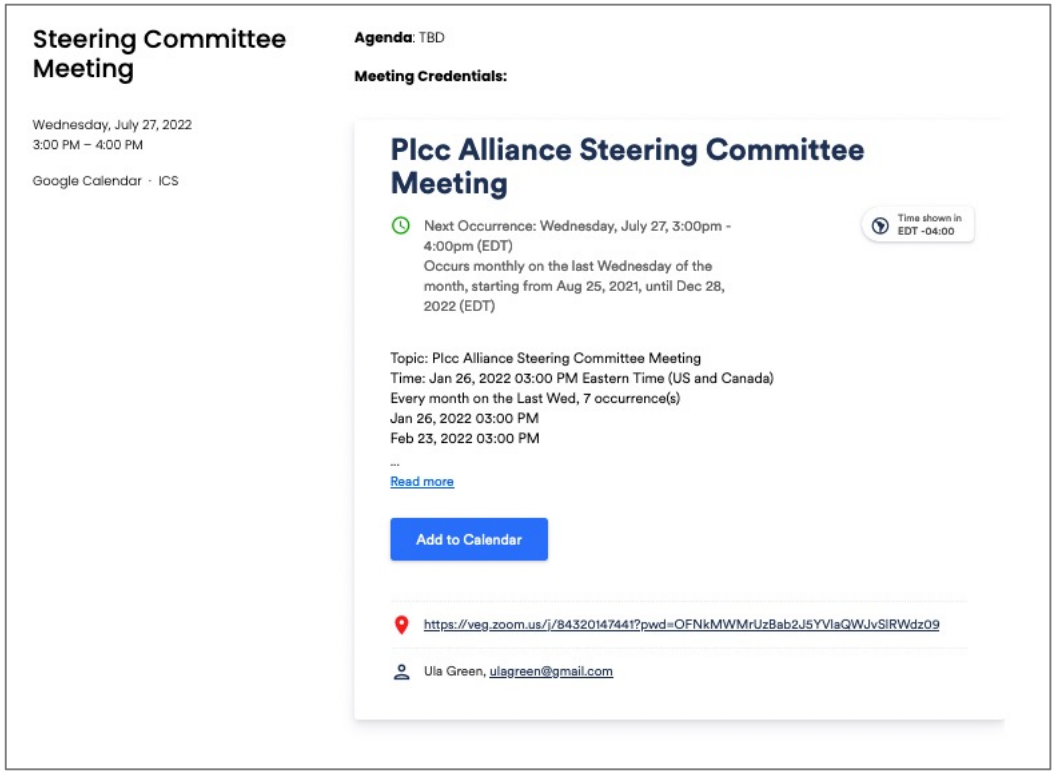
DRAFT

REVIEW

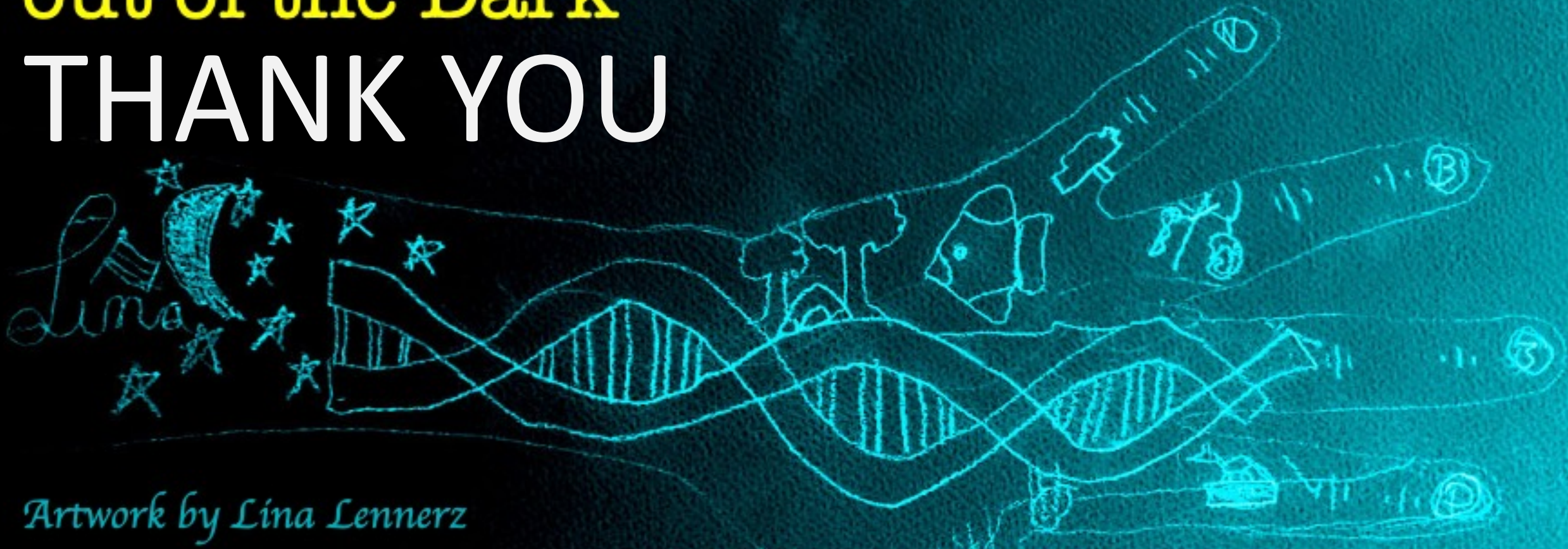
COMMENT

NEXT MEETING

Other events – NEXT week ☺



ctDNA
out of the Dark
THANK YOU



Artwork by Lina Lennerz