Expanding Clinical Trial Eligibility to Include Relevant Populations

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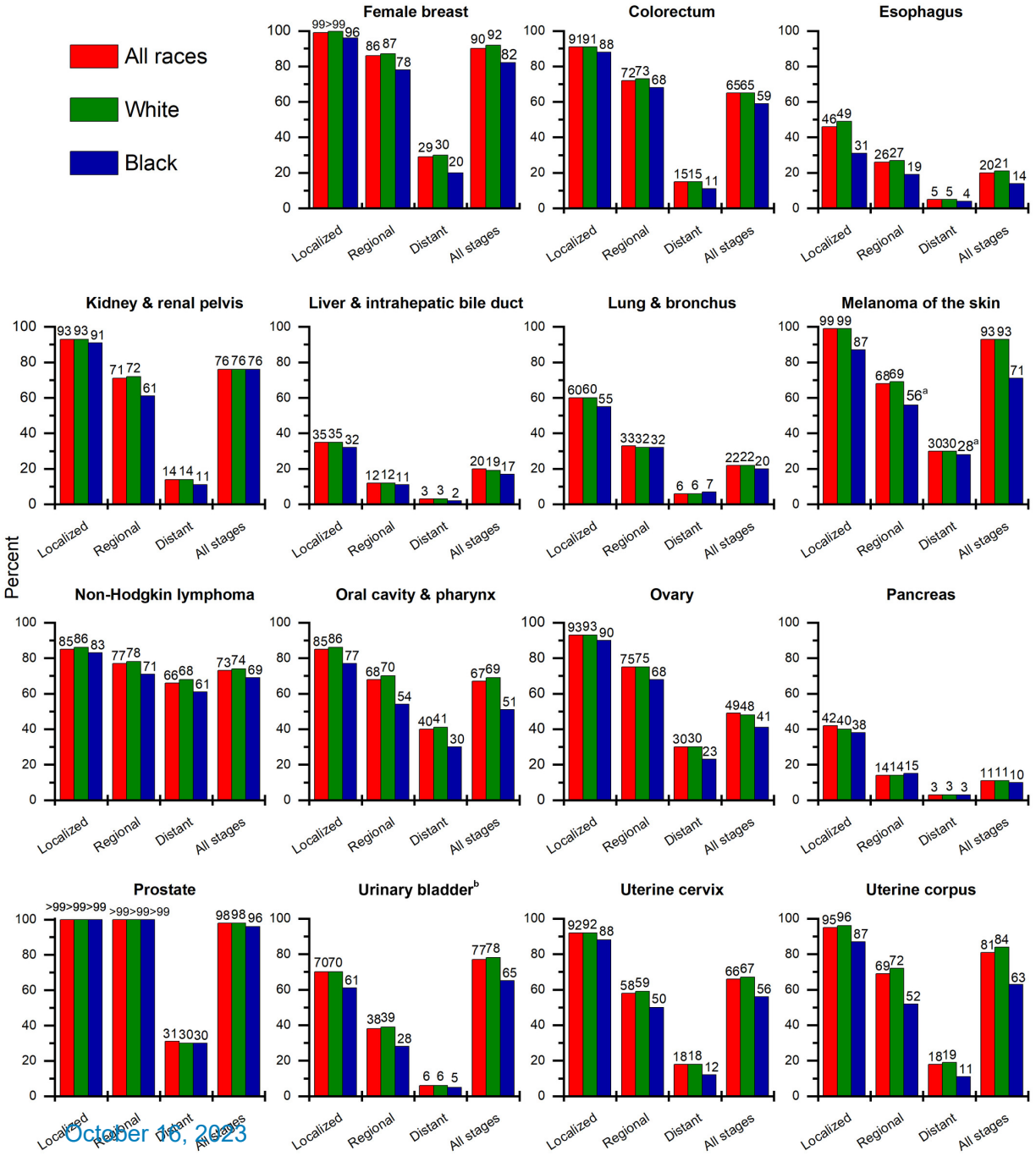
Why Do We Conduct Clinical Trials

- Generate data to inform safe & effective use of Medical Products
  - For the intended population
- Provide access to potentially promising medical products
  - Quick access important for patients
  - Clinical trials may provide a treatment option in some diseases

Differences in Outcomes by Race and Ethnicity



Disparities in the Incidence and Death rates between African American and Whites for Select Cancer Types

INCIDENCE RATES*			
Cancer Type	**African Americans**	**Whites**	**Rate Ratio**
Multiple myeloma	14.3	6.4	2.23
Prostate, males	172.8	102.0	1.69
Stomach	9.6	5.7	1.68
Liver and intrahepatic bile duct	11.9	7.4	1.61
Colorectal	45.5	36.5	1.25
Pancreas	15.7	12.7	1.24
Kidney and renal pelvis	19.2	15.7	1.22
Cervix uteri, females	7.4	6.3	1.17
Lung and bronchus	57.4	51.0	1.13
Breast, females	128.2	132.7	0.97

DEATH RATES*			
Cancer Type	**African Americans**	**Whites**	**Rate Ratio**
Prostate, males	38.4	18.2	2.11
Stomach	5.3	2.6	2.04
Multiple myeloma	6.0	3.0	2.00
Cervix uteri, females	3.1	2.2	1.41
Breast, females	27.3	19.6	1.39
Colorectal	18.3	13.4	1.37
Liver and intrahepatic bile duct	8.5	6.3	1.35
Pancreas	13.3	11.0	1.21
Lung and bronchus	40.2	39.3	1.02
Kidney and renal pelvis	3.4	3.7	0.92

*Both sexes unless otherwise specified

Data from: SEER Cancer Statistics Review 1975-2016 (Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER website, April 2019.

Five-Year Relative Survival for Selected Cancers by Race and Stage at Diagnosis, United States, 2011 to 2017.

AACR Cancer Disparities Progress Report 2020;

CA A Cancer J Clinicians, Volume: 72, Issue: 1, Pages: 7-33, First published: 12 January 2022

Oncology Clinical Trials: Inclusion vs. Equity

- Approximately 2-5% of adult cancer patients enroll in CT
- In 2020, 4,922 patients participated in oncology CT
- Of patients with cancer who participated in clinical trials (2004-15) for newly approved oncology drugs
  - Disproportionate Whites vs. Asians, Hispanics and Blacks
  - Enrollment favors young, healthy, metastatic, private insurance, academic medical centers

Table 1. Demographic and Clinical Characteristics

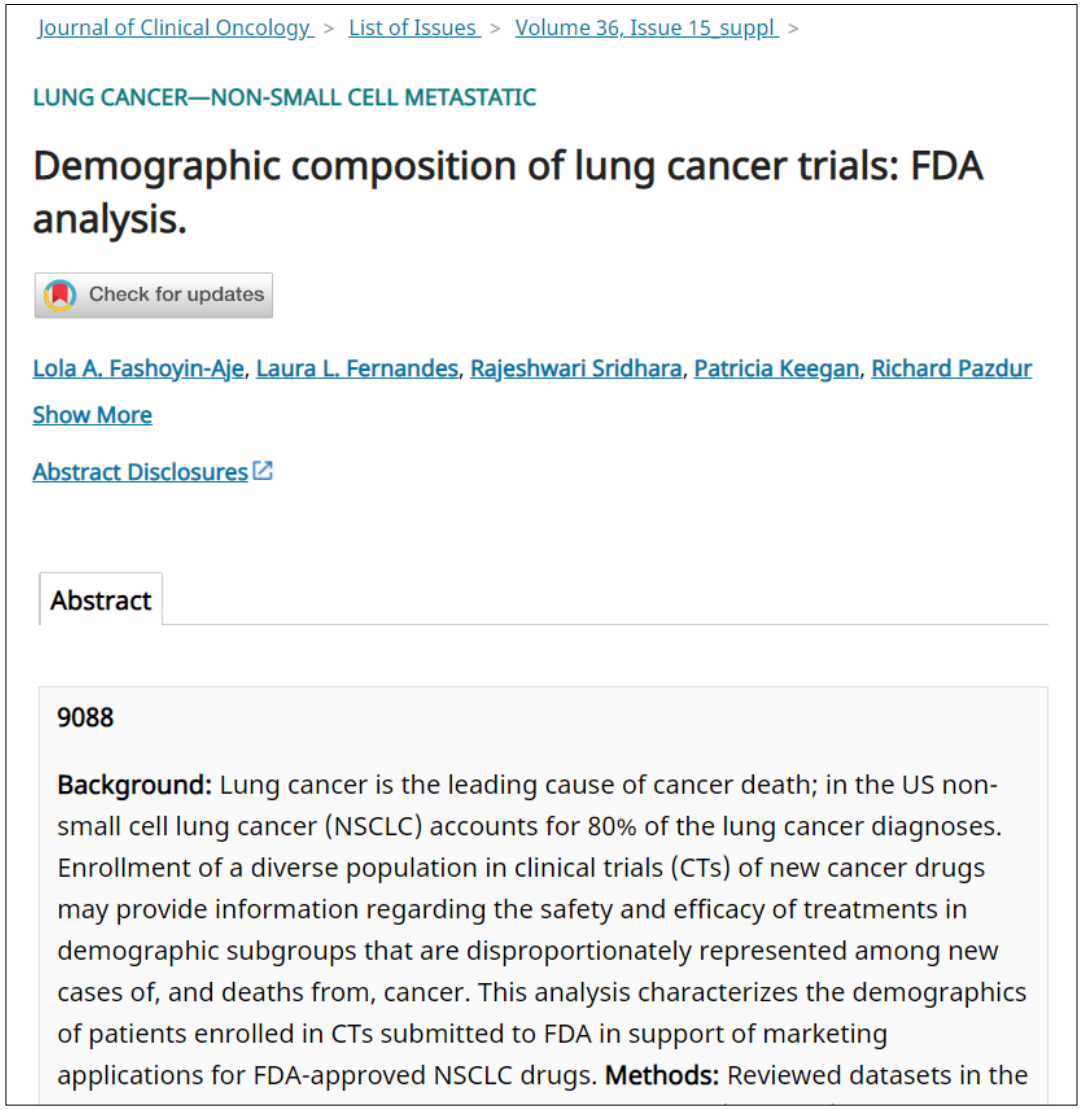
Characteristic	Enrolled n (%)	Not Enrolled n (%)
Patients, N	11,576	12,086,105
Age, median (IQR), y	59 (51–68)	65 (55–74)
Sex		
Male	5,931 (51.2)	6,499,323 (53.8)
Female	6,445 (48.8)	5,586,782 (46.2)
Race		
White	10,183 (88.0)	10,252,942 (84.8)
Black	823 (7.1)	1,266,023 (10.5)
Other	570 (4.9)	567,140 (4.7)

- Longer median overall survival for those in trials

Zaorsky NG. 2019
https://doi.org/10.6004/jnccn.2019.7321

Graphic from "Better Health for All"

Differences in Outcomes by Race and Ethnicity



Journal of Clinical Oncology > List of Issues > Volume 36, Issue 15_suppl >

LUNG CANCER—NON-SMALL CELL METASTATIC

Demographic composition of lung cancer trials: FDA analysis.

Check for updates

Lola A. Fashoyin-Aje, Laura L. Fernandes, Rajeshwari Sridhara, Patricia Keegan, Richard Pazdur

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Abstract Disclosures

Abstract

9088

Background: Lung cancer is the leading cause of cancer death; in the US non-small cell lung cancer (NSCLC) accounts for 80% of the lung cancer diagnoses. Enrollment of a diverse population in clinical trials (CTs) of new cancer drugs may provide information regarding the safety and efficacy of treatments in demographic subgroups that are disproportionately represented among new cases of, and deaths from, cancer. This analysis characterizes the demographics of patients enrolled in CTs submitted to FDA in support of marketing applications for FDA-approved NSCLC drugs. **Methods:** Reviewed datasets in the

- Representation of REM (<1%) lower than predicted by incidence

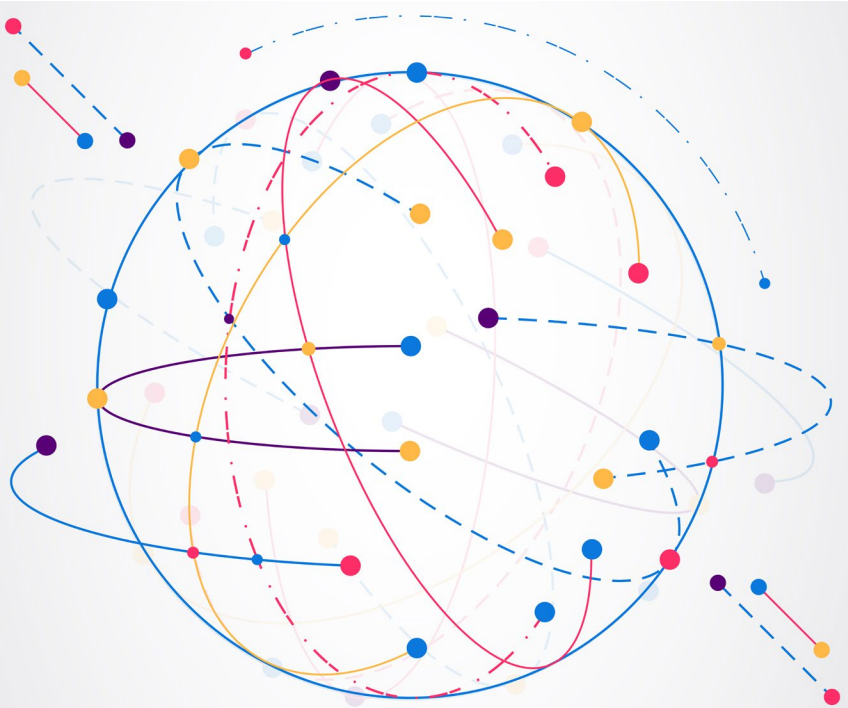
Enrollment by Trial Site

	All N=9711%	US N=1149%
American Indian/Alaskan Native	<1	<1
Asian	43	10
Black	<1	2
Native Hawaiian/Other Pacific Islander	<1	<1
White	50	82
Hispanic	2	3

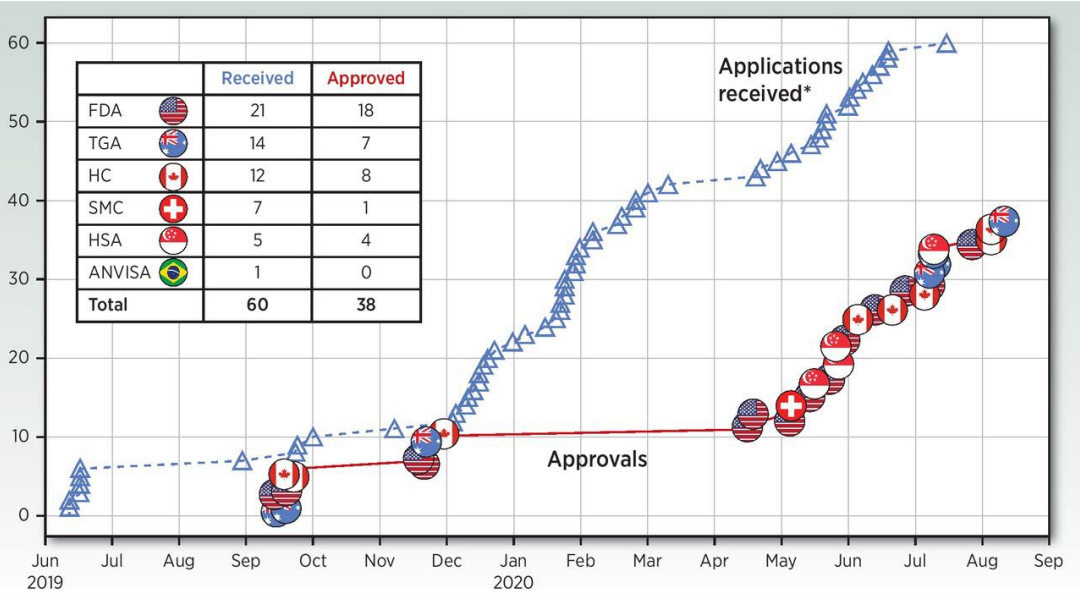
Fashoyin-Aje LA. 2018
DOI: 10.1200/JCO.2018.36.15_suppl.9088 Journal of Clinical Oncology

Racial/ethnic minorities in Clinical Trials – Contributing Factors

- Clinical trials are global
  - Approx. 20% of patients are enrolled from the U.S.
  - US racial/ethnic categories may not be applicable outside US
    - Ethnicity frequently not reported
  - Lack of diversity in global trial sites
- Trials enrolling patients entirely outside the US may support approval in the U.S.
- Impact is Global



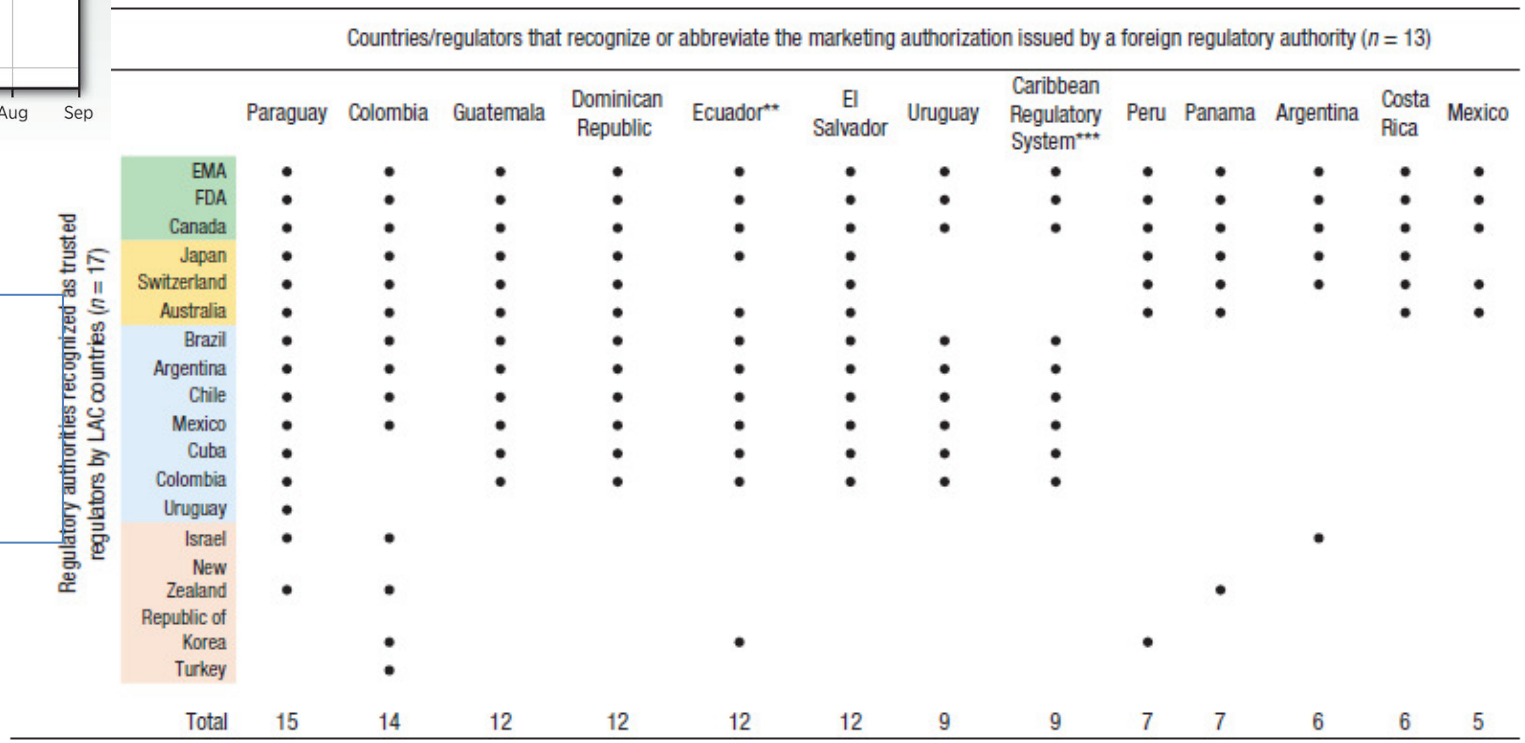
FDA Drug Approvals and Global Impact



Increased diversity in the countries that leverage Project Orbis

- Faster global drug approvals

Countries leverage approvals by other regulatory Agencies



De Claro RA 2020. doi: 10.1158/1078-0432.CCR-20-3292

Duran, CE 2021 doi: 10.26633/RPSP.2021.10

Many Ongoing Efforts to Increase Diversity and Equity

Clinical Trial Diversity: Data Points to Structural, Not Patient-Specific Solutions

25 Aug 2021 | NEWS

Clinical Trial Diversity Measures Primed For Inclusion In US FDA User Fee Legislation

17 Mar 2022 | NEWS

by Sue Sutter

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Executive Summary

House subcommittee hears testimony on merits of various proposals to increase diversit clinical trial participants; whether lawmakers ultimately favor measures that impose enf obligations on sponsors, or merely incentivize more diverse enrollment, remains to be se

WH.GOV

- **To address inequities** — Today, we know cancer as a disease for which there are stark inequities in access to cancer screening, diagnostics and treatment across race, gender, region, and resources. We can ensure that every community in America – rural, urban, Tribal, and everywhere else – has access to cutting-edge cancer diagnostics, therapeutics, and clinical trials.
- **To target the right treatments to the right patients** — Today, we know cancer as a disease for which we understand too little about why treatments work for some patients, but not for others. We are learning more about how to use information about genetics, immune responses, and other factors to tell which combinations of treatments are likely to work best in an
- **To learn from all patients** — Today, we know cancer as a disease in which we don't learn from the experiences of most patients. We can turn our cancer care system into a learning system. When asked, most people with cancer are glad to make their data available for research to help future patients, if it can be done easily while respecting their privacy. Additionally, the diverse personal experiences of patients and their families make their input essential in developing approaches to end cancer as we know it.

Importance of Clinical Trial (CT) Diversity

- Diversity facilitates generalizability of study results
  - Implement measures to improve evidence generation for **underrepresented demographic** in medical product development programs, to characterize outcomes in across patients using approved therapeutics.

- Need to evaluate drugs in context of variability in population
  - Differential PK across population
  - Differential MP response (efficacy and safety) across the population
  - Differential presentation of disease/condition across diverse population

- Lack of data ≠ Lack of difference
  - Data needed to characterize parameters (e.g., drug metabolism, disease biology, etc.,) that may result in clinically important differences in safety &/or efficacy by race or ethnicity

Contains Nonbinding Recommendations

Draft — Not for Implementation

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

https://www.fda.gov/media/157635/download

Conclusion

- We develop drugs for patients not the other way around
- Diversity is very important to understand differences in drug PK, and activity
- Thoughtful considerations through the diversity plan can help us prospectively achieve these goals

Diversity allows us to embrace our goal of the “right drug, right patient, right time, and right dose”


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Should Clinical Pharmacologist Ignore the Diversity Plan

- Provides an opportunity to collect data to identify and/or characterize PK, PD, pharmacodynamic differences
- Consider the limitations of small sample size on identifying or ruling out true differences

V. CONTENT OF THE RACE AND ETHNICITY DIVERSITY PLAN (THE PLAN)

- Sponsors should define enrollment goals for underrepresented racial and ethnic participants as early as practicable in clinical development for a given indication. These enrollment goals should be based in part on the pre-specified protocol objectives of the investigation. While in many cases race- and/or ethnicity- defined populations may be genetically heterogenous such that analyses to characterize differential effects due to pharmacogenomic variability may be difficult to discern, the Plan should begin with an assessment of any data that may indicate the potential for a medical product to have differential safety or effectiveness associated with race or ethnicity. For drug development, as applicable to the particular drug, the collection of sufficient pharmacokinetic (PK), pharmacodynamic (PD), and pharmacogenomic data from a diverse population is strongly encouraged to inform analyses of drug exposure and response.[26] For devices, data on the relevant factors for device performance (e.g., phenotypic, anatomical, or biological) should be collected to inform any differential effects across a diverse population. For example, variations in skin pigmentation exist

Contains Nonbinding Recommendations

Draft — Not for Implementation

- The Plan should describe the planned assessment of race and ethnicity in addition to other covariates with known potential to affect the safety and effectiveness of the medical product. In particular, for drugs, covariates with known potential to affect PK and PD should be assessed in order to facilitate exposure-response analyses and to inform safe and effective dosing regimens across the intended patient population, as applicable. For devices, device performance may be impacted by factors associated with race (e.g., the ability of a device to detect skin cancer based on skin pigmentation).

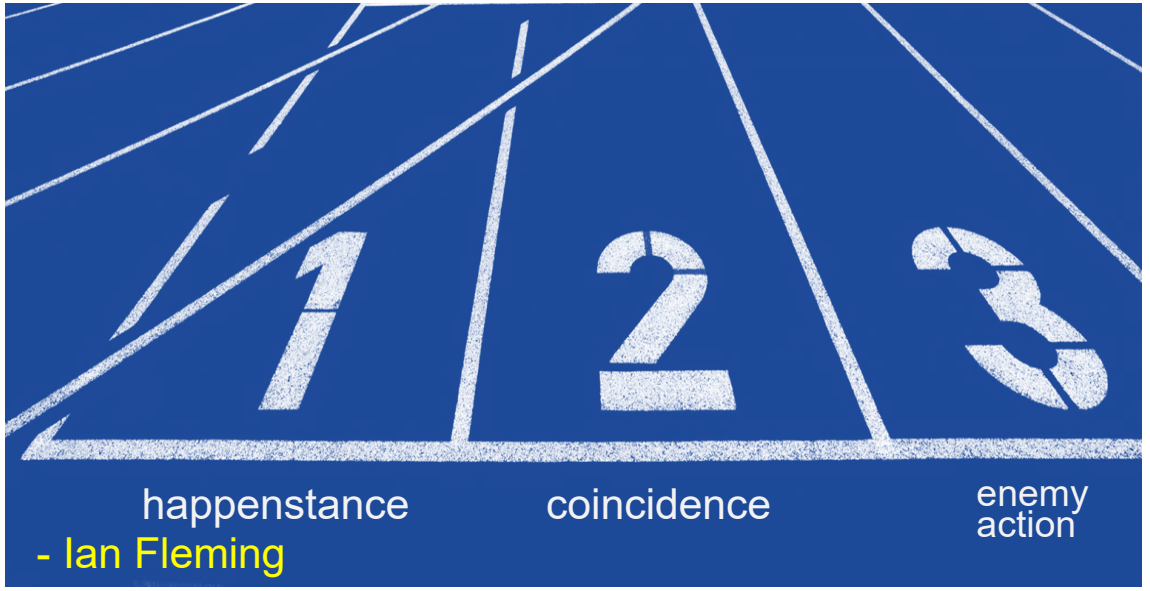
- Provides an opportunity to collect data for more robust exposure-response analyses for efficacy and safety
- Generate information important to HCP and patients

Clinical Pharmacology and the Diversity Plan

When there are data that indicate that the medical product may perform differentially across the population based on factors associated with race or ethnicity, the Plan should specify the study design features that will support analyses that will inform the safety and effectiveness of the medical product in the relevant racial and ethnic populations. In some cases, increased (i.e., greater than proportional) enrollment of certain populations may be needed to elucidate potential important differences. When there are no data that indicate that race or ethnicity will impact safety or effectiveness, it is nonetheless appropriate that enrollment reflects the epidemiology of the disease. FDA recognizes that enrollment based on epidemiology alone may not be sufficient to detect any differences in safety and effectiveness or make such inferences; however, consistent representative enrollment may provide opportunities for pooling data to evaluate outcomes by race and ethnicity.

Does not imply conducting clinical studies when there is no clinical pharmacology basis to support it

Consistent generation of data helps us observe patterns that small sample sizes may hide, or that we may misinterpret



https://www.fda.gov/media/157635/download

Clinical Pharmacologist and the Diversity Plan

- The Plan should outline the sponsor's plan to collect data to explore the potential for differences in safety and/or effectiveness associated with race and ethnicity throughout the entire development life-cycle of the medical product and not just during the pivotal trial(s) or studies.

https://www.fda.gov/media/157635/download

- Trends in PK, safety and efficacy can be observed early.
- Can pivot to an enrichment trial, if necessary
- Can identify areas that may be worth exploring, for the drug class, indication, or mutation or population

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- Brian Booth, Ph.D
- Anu Ramammoorty, PhD

- Members of Project Equity
- Division of Cancer Pharmacology I and II
- Oncology Center of Excellence
- Office of Clinical Pharmacology

Racial/Ethnic Minorities in Clinical Trials

- Racial/ethnic minorities underrepresented in clinical research
  - Clinical trials supporting approval of cancer therapeutics: less than 10% patients are racial/ethnic minorities

FDA 2020 Drug Trials Snapshots (oncology)	US Census Population Estimates (2019)
White 73%	White 76%
Black 5%	Black 13%
Asian 14%	Asian 6%
Hispanic 6%	Hispanic 19%

Leveraging Clinical Pharmacology to Identify Knowledge Gaps and Bridge Available Information Across Subpopulations

Where are we?

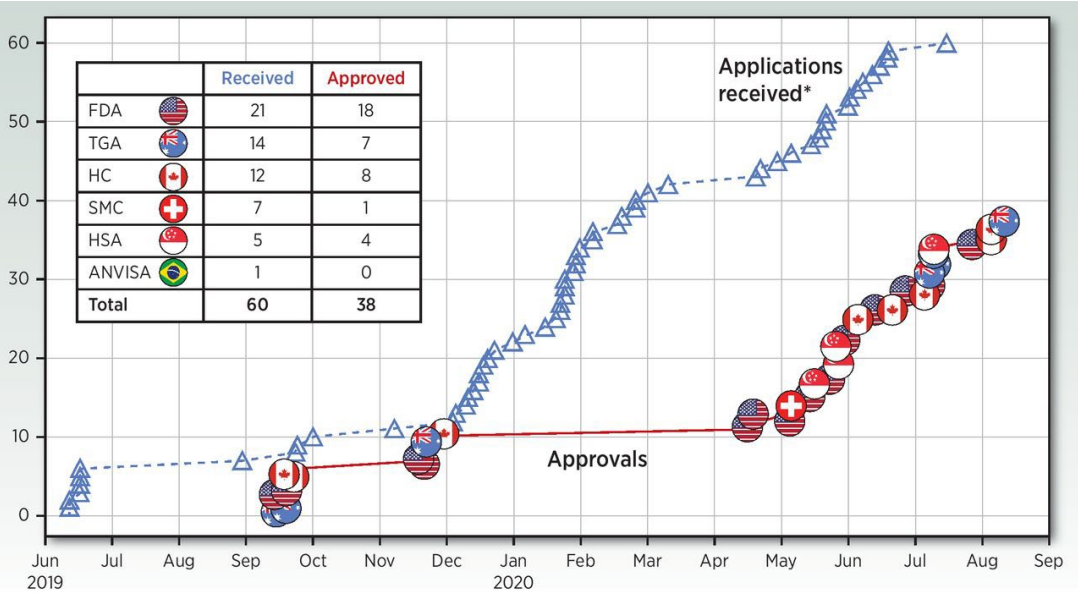
- Limited information from racial and ethnically diverse patients in clinical studies
- Limited heterogenicity in clinical trials, including dose finding and expansion studies
- Lack of data to associate differences in clinical outcomes
  - Unknown differences in efficacy and safety

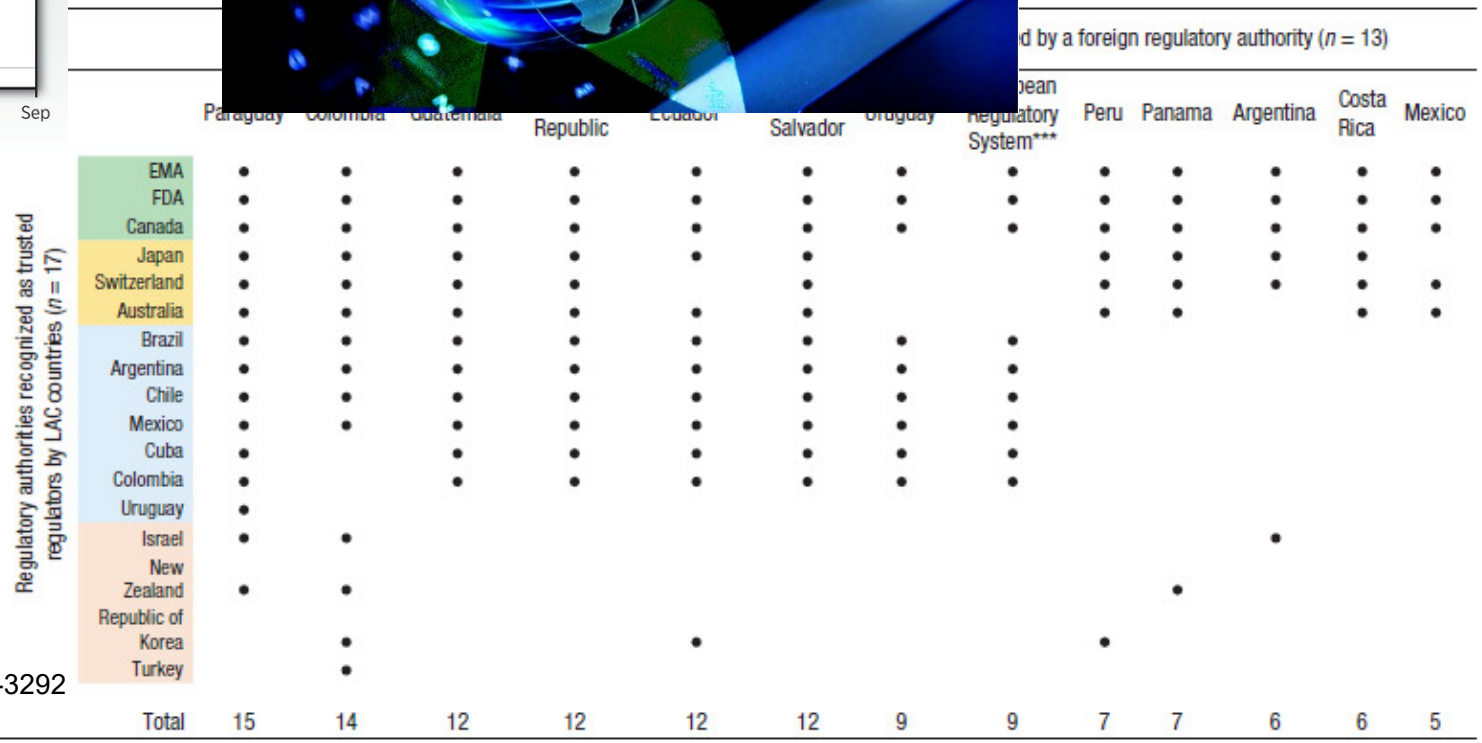
Where are we going?

- Right drug, right dose, **right patient**

- Working with and leveraging the opportunity provided with the Diversity Plan will help us get there

FDA Drug Approvals and Global Impact





Clin Cancer Res. 2020;26(24):6412-6416. doi: 10.1158/1078-0432.CCR-20-3292

doi: 10.26633/RPSP.2021.10