The Association of Maternal *HBB* Pathogenic Variant Status and Fetal Fraction in Non-invasive Prenatal Screening

Manesha Putra, MD, Kristjan Eerik Kaseniit, PhD, Melissa Hicks, MS,
Dale Muzzey, PhD, and David Hackney, MD, MS

Presented at SMFM on February 3-8, 2020

MetroHealth
SCHOOL OF MEDICINE CASE WESTERN RESERVE UNIVERSITY
University Hospitals MacDonald Women's Hospital

Disclosure

MP, MAH and DH

No conflict of interest

KEK and DM

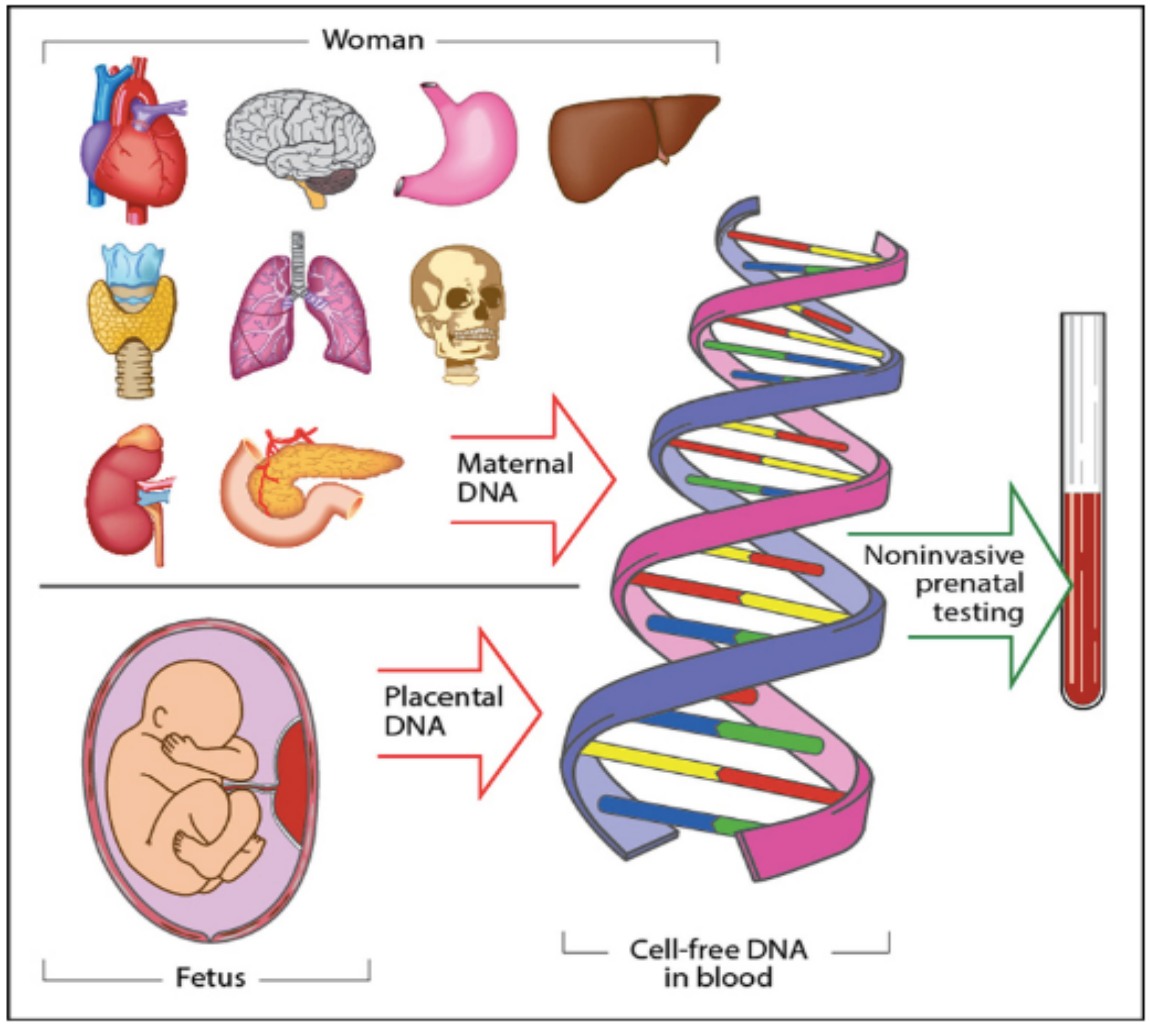
Employed by Myriad Genetics, Inc, Salt Lake City, UT

Data obtained from Myriad Genetics

Participated in study design and data analysis

Not involved in final editorial decisions

Non-Invasive Prenatal Screening (NIPS)
Fetal Fraction (FF)



Skrzypek et al, 2017
Liang et al, 2018

MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women's Hospital

Factors Affecting FF

Fetal influences
Gestational age
Multiple gestation
Fetal aneuploidy

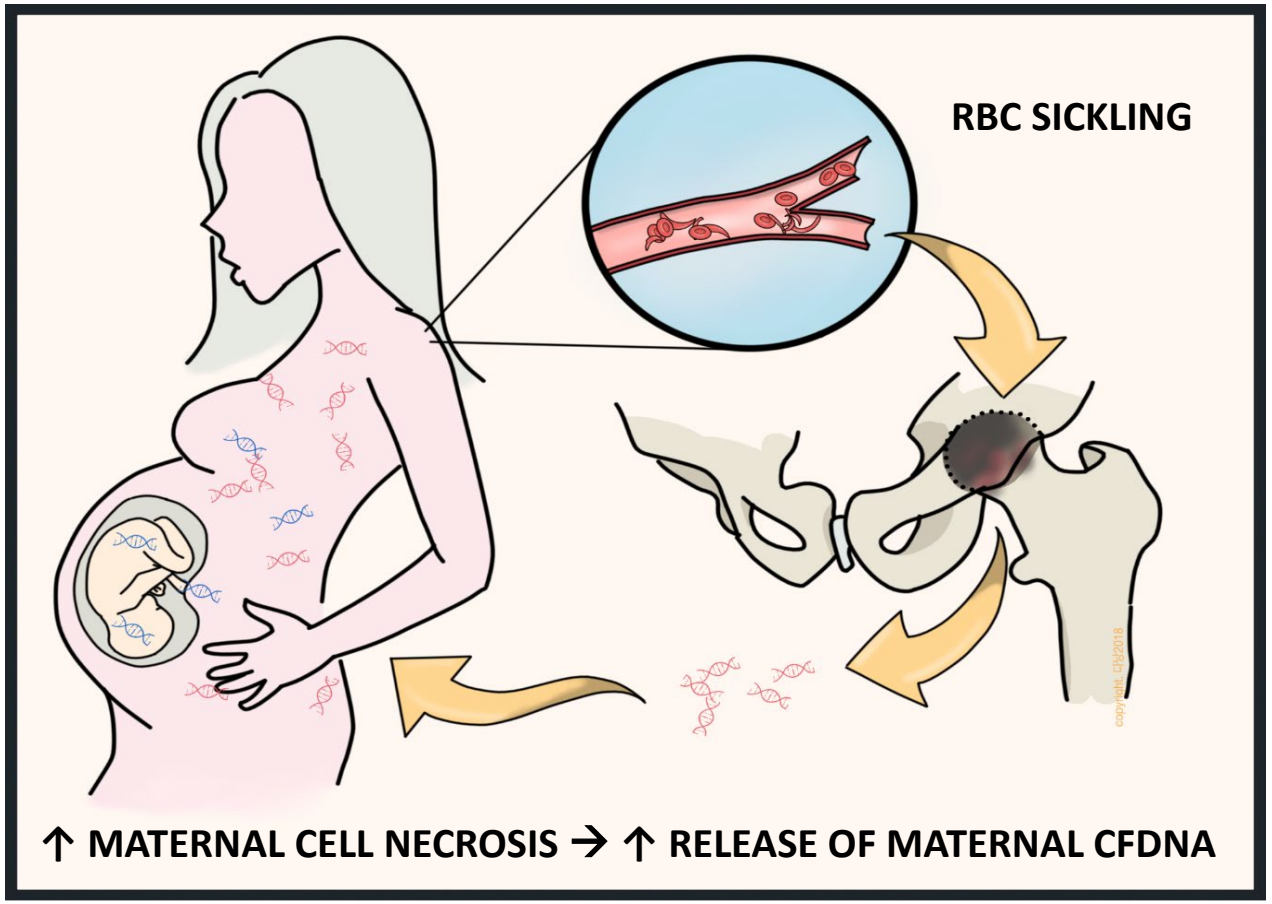
$$Fetal\ fraction = \frac{fetal\ cfDNA}{fetal\ cfDNA + maternal\ cfDNA}$$

Maternal Influence
Body mass index
Maternal medical conditions

Taglauer et al, 2014

Women With *HBB* Hemoglobinopathies Have Lower Fetal Fraction

"5x increase no-call rate"



Putra et al, 2019

HBB gene carrier may have mild-severe clinical manifestations

Sickle Cell Trait

Definite Associations →

Renal medullary cancer
Hematuria
Renal papillary necrosis
Splenic infarction
Exercise-related sudden death

Kotila et al, 2016
Tsaras et al, 2009

Objectives

To determine if:

1) *HBB* pathogenic variant carrier status is associated with altered Fetal Fraction in Maternal blood from NIPS samples
2) *HBB* pathogenic variant carrier status is associated with an altered rate of “No-Call” results

Study Design

Retrospective cohort study

Myriad NIPS and carrier screening lab database 2016-2019

β-globin group — NIPS and β-globin (*HBB)* hemoglobinopathy carrier
- Structural (eg. Hemoglobin S, C, E trait)
- Quantitative (beta-thalassemia minor and trait)

α-globin group — NIPS and α-globin *(HBA1/HBA2)* hemoglobinopathy carrier
- alpha-thalassemia silent carrier and trait

Comparison group — NIPS and non-carrier of **β-globin/α-globin**

Study Design

Exclusion criteria

β-globin and α-globin hemoglobinopathies

FF was adjusted using multivariate linear regression

Covariates: maternal age, gestational age, BMI → corrected FF

β-globin subgroup analyses

Hemoglobin S hemoglobinopathy carriers

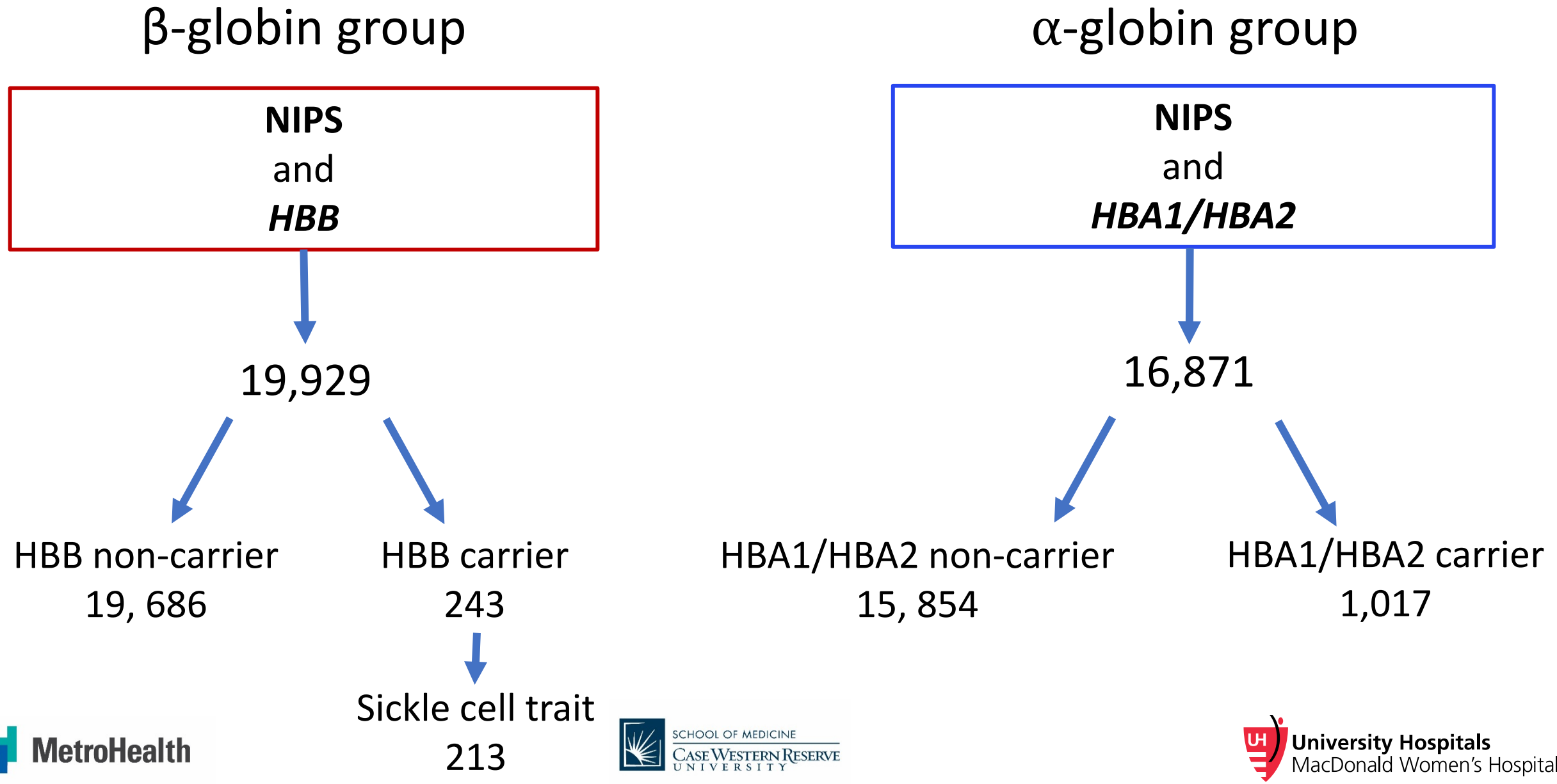
Statistical Analysis

Kolmogorov-Smirnov test

Cohort Distributions

Estimate of no-call rate for hypothetical FF cutoffs

Study Cohorts



MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women's Hospital

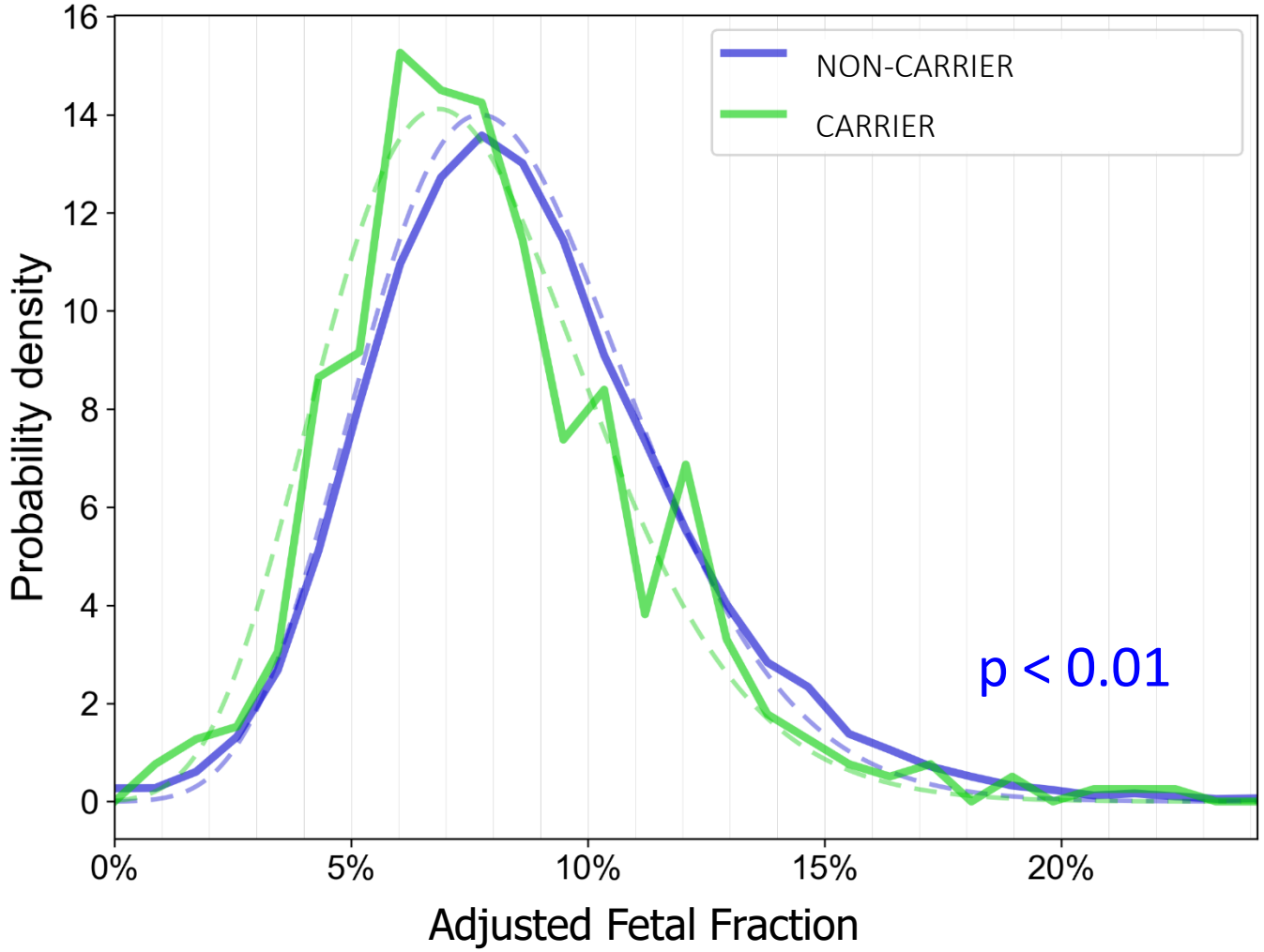
β-globin Group

Demographic Characteristics
β-Globin

	β-Globin Carriers	β-Globin Non-Carriers
	Median [IQR]	
Maternal Age	32 [27-36]	33 [29-36]
Gestational Age	12.6 [11.6-14.3]	12.1 [11.0-13.1]
BMI	26.8 [23.2-31.5]	25.2 [22.3-29.5]

Fetal Fraction Distribution

β-Globin



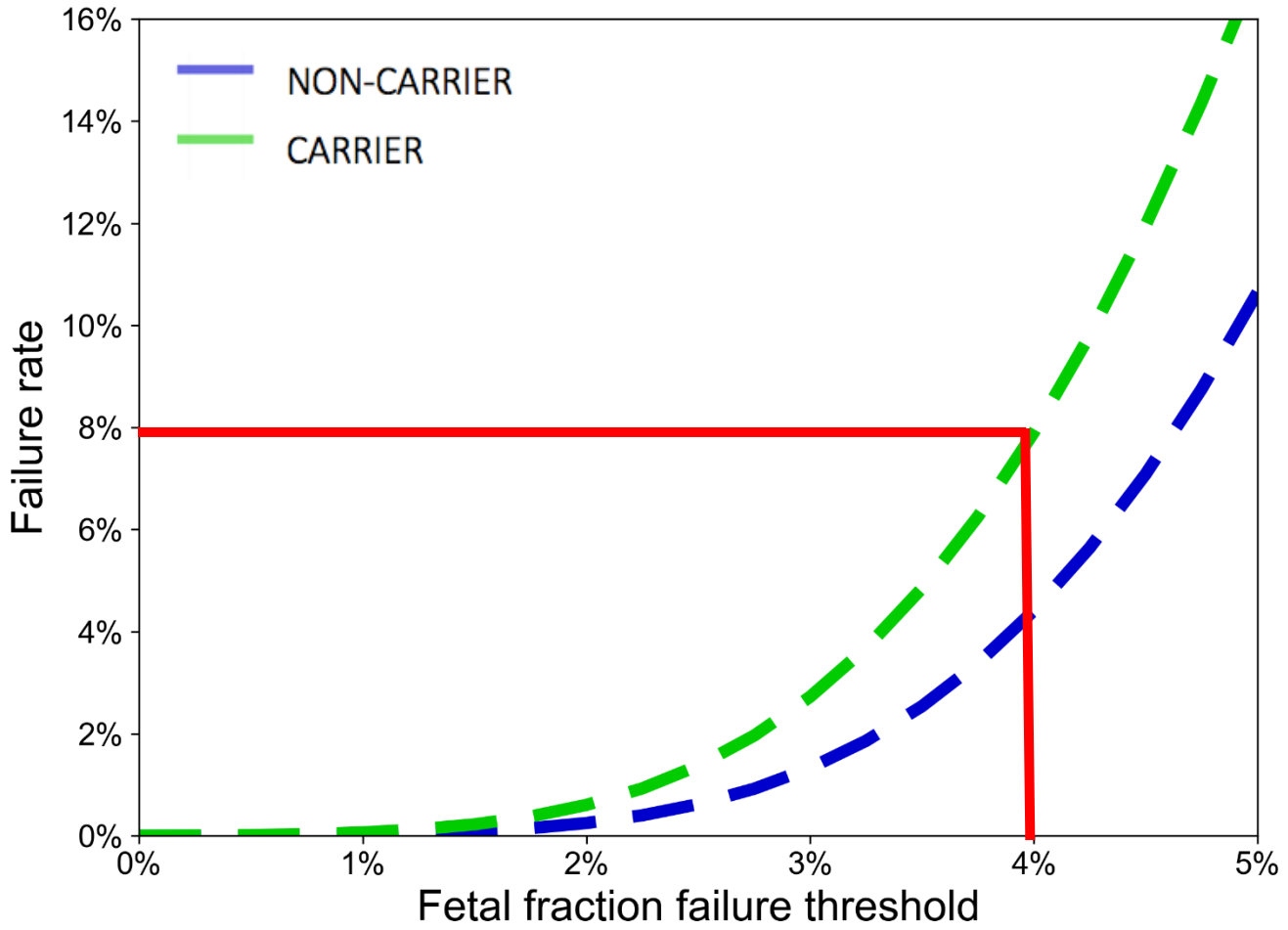
MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women's Hospital

Expected “No-Call” Rate

β-Globin



β-globin Subgroup Analyses: Hemoglobin-S carrier

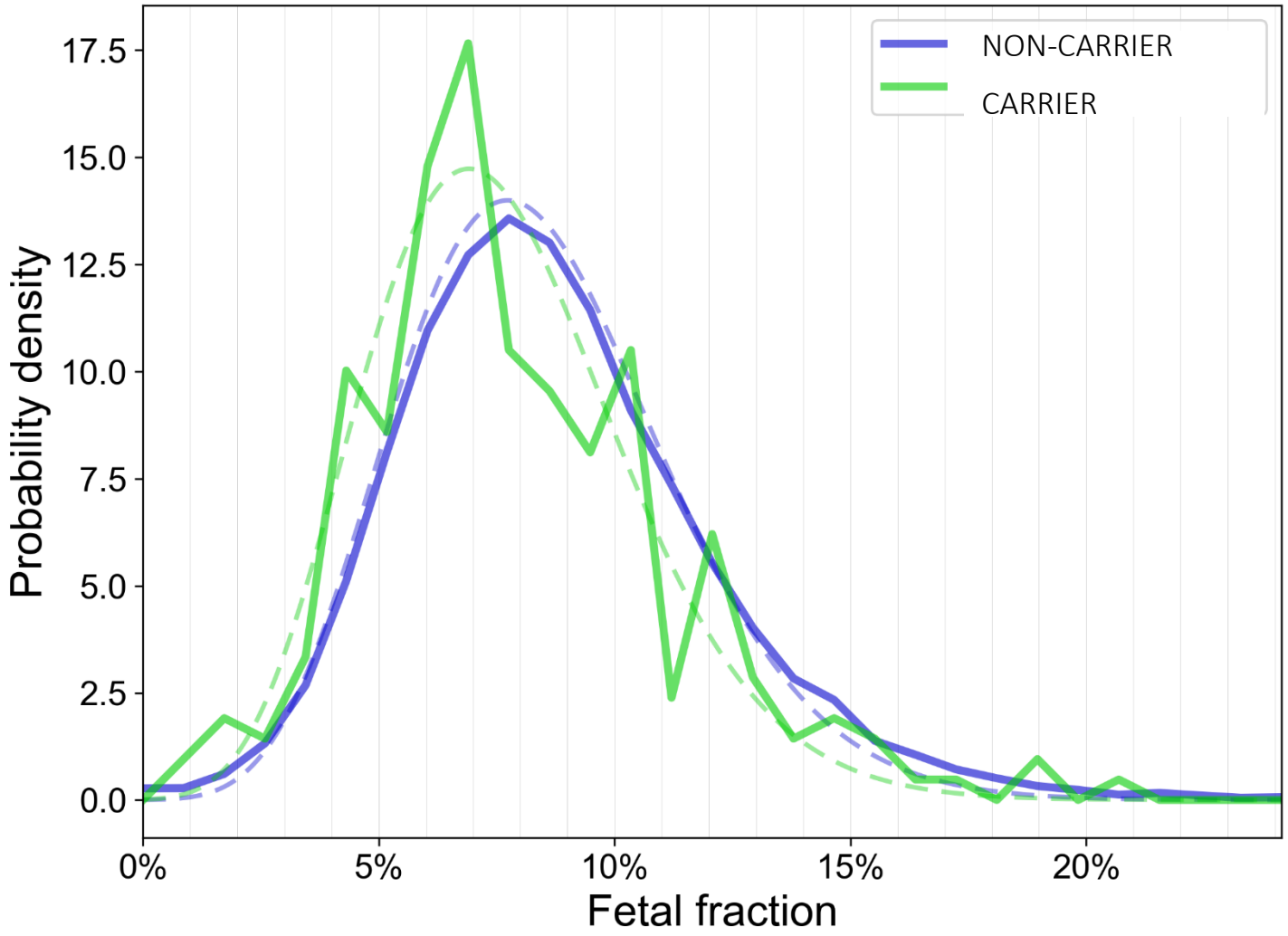
Demographic Characteristics

Sickle Cell Trait

	Sickle Cell Trait	Non-Carrier
	Median [IQR]	
Maternal age	31 [25-36]	33 [29-36]
Gestational age	12.9 [11.7-14.7]	12.1 [11.0-13.1]
BMI	28.3 [24.7-33.5]	25.2 [22.3-29.5]

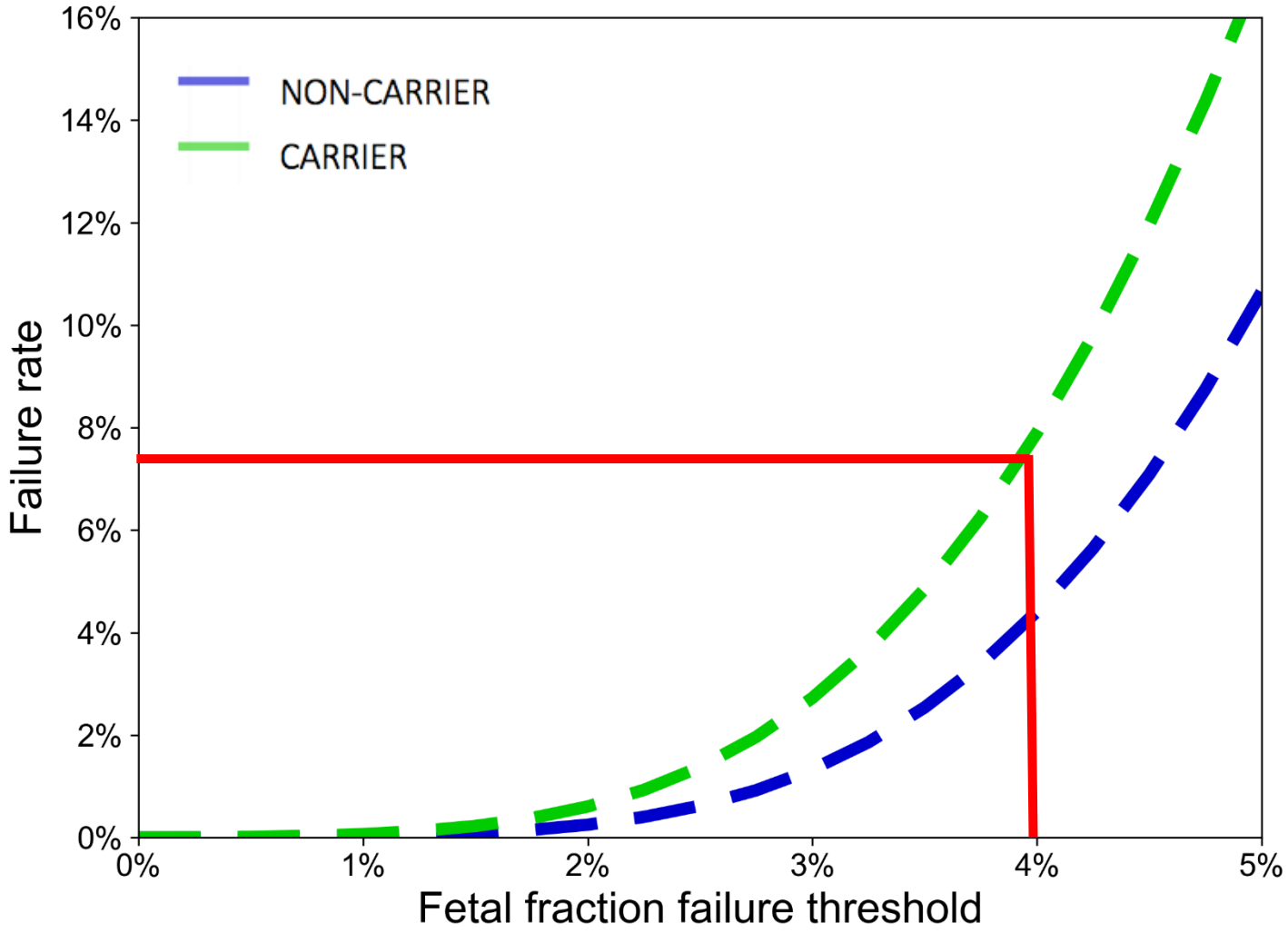
Fetal Fraction Distribution

Hemoglobin S carrier



Expected “No-Call” Rate

Hemoglobin-S carrier



MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women’s Hospital

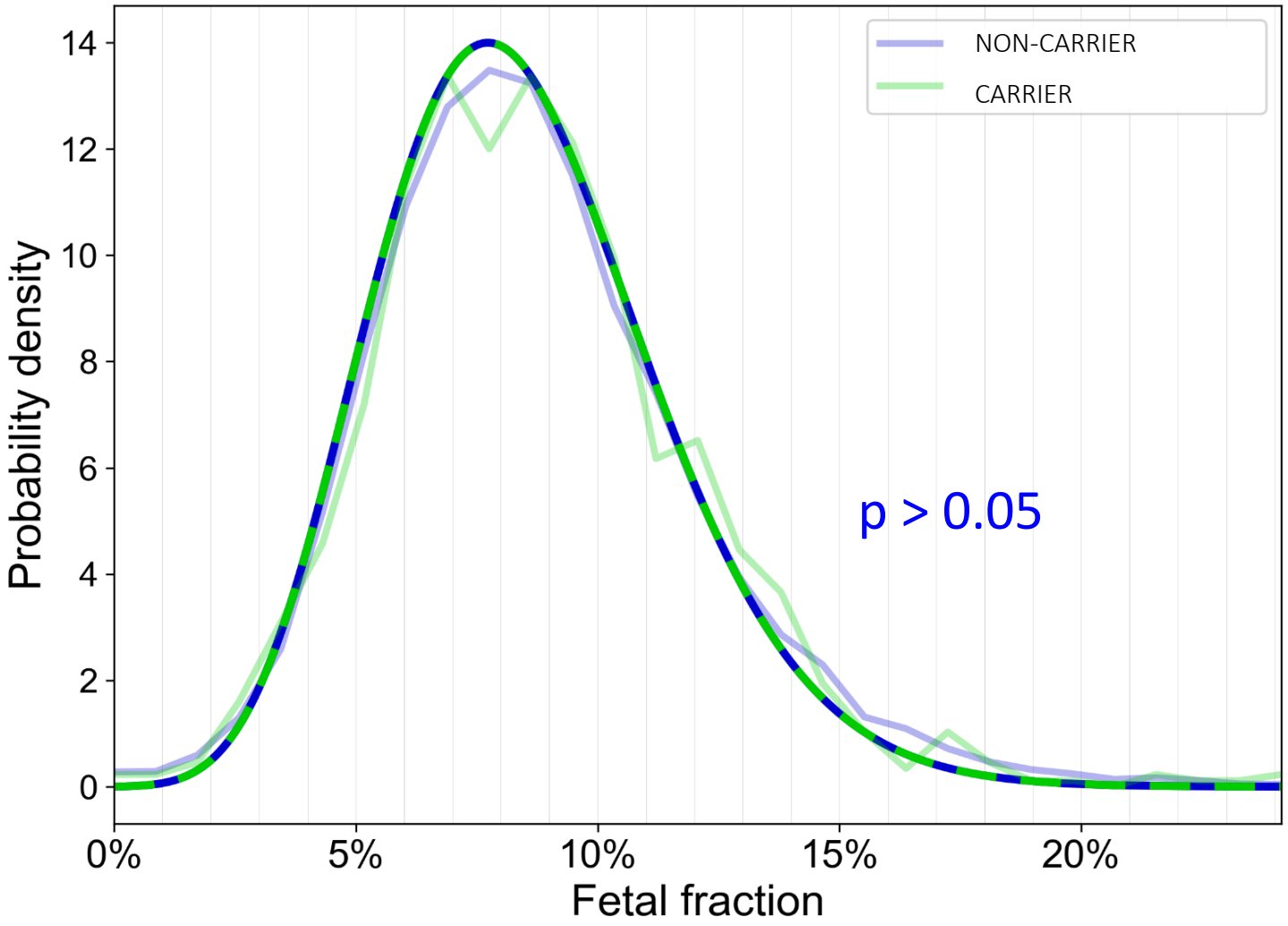
α-Globin Group

Demographic Characteristics
α-Globin

	α-Globin Carriers	α-globin Non-Carriers
	Median [IQR]	
Maternal Age	32 [27-36]	33 [29-36]
Gestational Age	12.6 [11.3-13.9]	12.1 [10.9-13.1]
BMI	26.5 [22.9-31.6]	25.1 [22.2-29.5]

Fetal Fraction Distribution

α-Globin



MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women's Hospital

Conclusions

β-globin carriers

Lower FF and higher no-call rate

Sickle cell traits

Lower FF and higher no-call rate

α-globin carriers

No difference in FF and no-call rate

Implications

If confirmed on further studies, should be considered in pre- and post-test counseling

Impact of fetal hemoglobinopathy status is unknown

Impact of maternal carrier status on risk of aneuploidy among “no-calls” is unknown

Acknowledgement

Brian Mercer, MD

Justin Lappen, MD

MetroHealth

SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

University Hospitals
MacDonald Women's Hospital

Additional Slides

Study Design

- NIPS: Whole-genome sequencing methodology
- β-globin carrier screening: Sequencing with copy number analysis
- α-globin carrier screening: Analysis of homologous regions

ETHNICITY INFORMATION FOR HBB Group

Carriers:

- South Asian: 10.70%
- Ashkenazi Jewish: 0.82%
- African or African American: 22.63%
- Southeast Asian: 16.05%
- unknown: 13.17%
- Caucasian Other: 16.87%
- Northern European: 2.47%
- Southern European: 4.94%
- Hispanic: 4.94%
- East Asian: 4.12%
- Middle Eastern: 3.29%

Non-carriers:

- Caucasian Other: 35.88%
- Hispanic: 9.12%
- unknown: 13.60%
- African or African American: 7.29%
- Northern European: 15.68%
- Southern European: 2.03%
- Ashkenazi Jewish: 3.28%
- East Asian: 4.79%
- South Asian: 3.88%
- Middle Eastern: 1.62%
- Southeast Asian: 1.92%
- French Canadian or Cajun: 0.43%
- Native American: 0.26%
- Pacific Islander: 0.19%
- Finnish: 0.03%

ETHNICITY INFORMATION FOR HBA1/HBA2 Group:

CARRIERS:
Hispanic: 9.33%
Ashkenazi Jewish: 1.87%
African or African American: 39.98%
Middle Eastern: 3.93%
Southeast Asian: 2.95%
Caucasian Other: 14.34%
East Asian: 4.22%
South Asian: 7.37%
unknown: 11.59%
Northern European: 2.95%
French Canadian or Cajun: 0.20%
Southern European: 1.08%
Pacific Islander: 0.20%

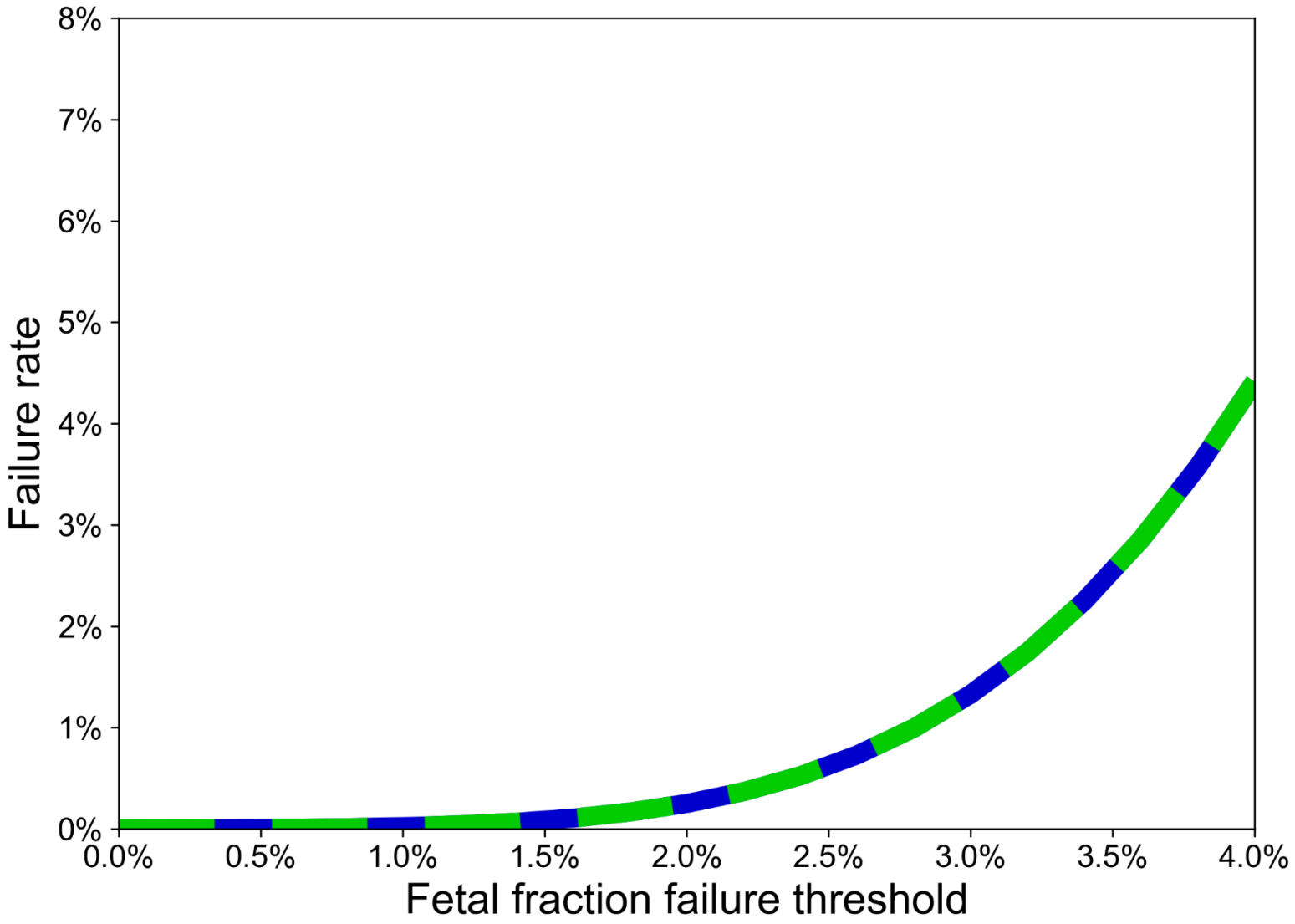
NON_CARRIERS:
Caucasian Other: 36.81%
Hispanic: 9.34%
African or African American: 5.33%
Northern European: 16.10%
Southern European: 1.91%
Ashkenazi Jewish: 3.20%
East Asian: 5.13%
unknown: 14.00%
South Asian: 3.73%
Middle Eastern: 1.54%
Southeast Asian: 1.96%
French Canadian or Cajun: 0.44%
Native American: 0.30%
Pacific Islander: 0.18%
Finnish: 0.03%

ETHNICITY INFORMATION FOR HbS PATIENTS:

CARRIERS:
Hispanic: 15.02%
Caucasian Other: 7.04%
African or African American: 62.44%
unknown: 11.27%
Middle Eastern: 0.47%
Southern European: 0.94%
Ashkenazi Jewish: 0.47%
Native American: 0.94%
East Asian: 0.47%
Northern European: 0.47%
French Canadian or Cajun: 0.47%

NON_CARRIERS:
Caucasian Other: 35.88%
Hispanic: 9.12%
unknown: 13.60%
African or African American: 7.29%
Northern European: 15.68%
Southern European: 2.03%
Ashkenazi Jewish: 3.28%
East Asian: 4.79%
South Asian: 3.88%
Middle Eastern: 1.62%
Southeast Asian: 1.92%
French Canadian or Cajun: 0.43%
Native American: 0.26%
Pacific Islander: 0.19%
Finnish: 0.03%

Probability of Non-reportable Results in *HBA1/HBA2* carriers



MetroHealth

University Hospitals
MacDonald Women's Hospital

HBB Statistics

	HBB carriers	HBB non-carriers
Maternal age	32 [27-36]	33 [29-36]
Gestational age	12.6 [11.6-14.3]	12.1 [11.0-13.1]
BMI	26.8 [23.2-31.5]	25.2 [22.3-29.5]
Fetal Fraction	7.9% [6.1%-10.1%]	8.6% [6.5%-11.2%]

HBA Statistics

-	HBA carriers	HBA non-carriers
Maternal age	31.5 ± 5.9	32.3 ± 5.3
Gestational age	13.6 ± 3.9	12.8 ± 3.2
BMI	27.8 ± 6.3	26.5 ± 5.7
Fetal Fraction	9.1% ± 3.8%	9.1% ± 3.8%

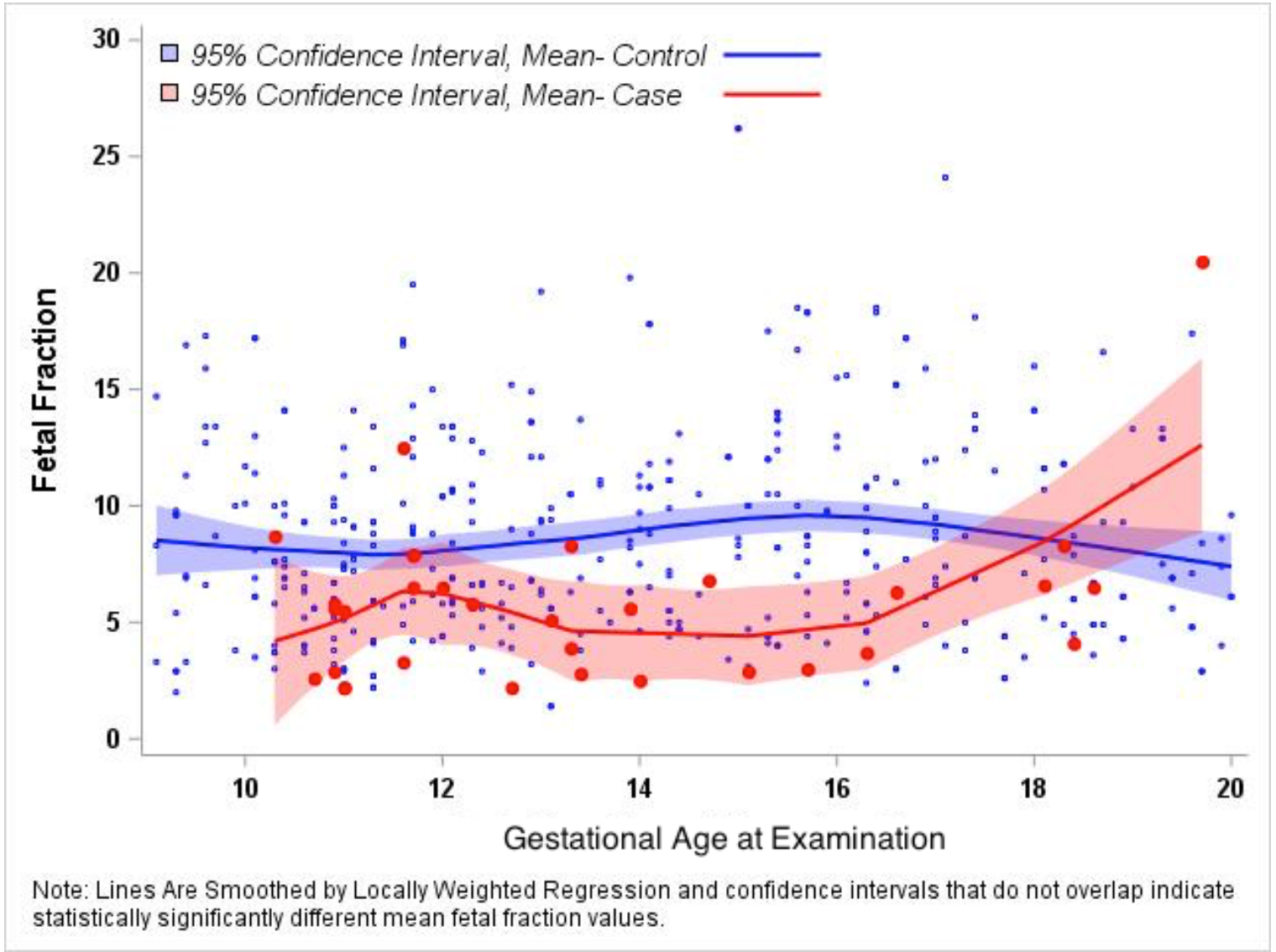
Non-HBS Statistics

-	HBB carriers of non-HbS variant	HBB non-carriers
Maternal age	32.6 ± 6.1	32.3 ± 5.3
Gestational age	13.5 ± 3.4	12.8 ± 3.1
BMI	26.6 ± 5.7	26.5 ± 5.7
Fetal Fraction	8.6% ± 3.7%	9.1% ± 3.8%

HBS Statistics

	HbS carriers (excluding affected)	HbS non-carriers
Maternal age	31 [25-36]	33 [29-36]
Gestational age	12.9 [11.7-14.7]	12.1 [11.0-13.1]
BMI	28.3 [24.7-33.5]	25.2 [22.3-29.5]
Fetal Fraction	7.7% [5.9%-9.8%]	8.6% [6.5%-11.2%]

Difference in fetal fraction in women with hbb hemoglobinopathies VS HEMOGLOBIN AA



MetroHealth

University Hospitals
MacDonald Women's Hospital

Methodology

Carrier Screening. β-globin carrier screening: Sequencing with copy number analysis and α-globin carrier screening: Analysis of homologous regions