Understanding autism spectrum disorder from placental chorionic surface vascular network

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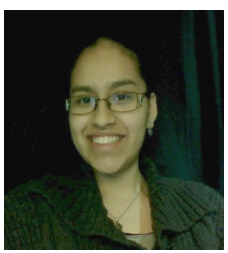
Disclaimer

- **ME:** "I am an **applied** **mathematician** who uses geometric methods to study large data sets, especially data sets that are digital photographs in nature."
- **YOU:** "So, why are you giving a talk that sounds so medical?"
- **ME:** "Well, if I had told you that my talk will be on 'Vessel enhancement with multi-scale and curvilinear filter matching for placenta images,' I am afraid that you wouldn't have come."

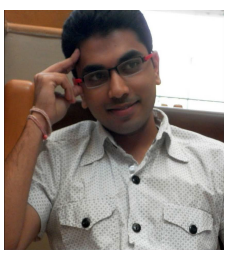
The work presented here is the $\sum$ of the following people's effort:

Carrie Salafia

Nen Huynh



Marilyn Vazquez

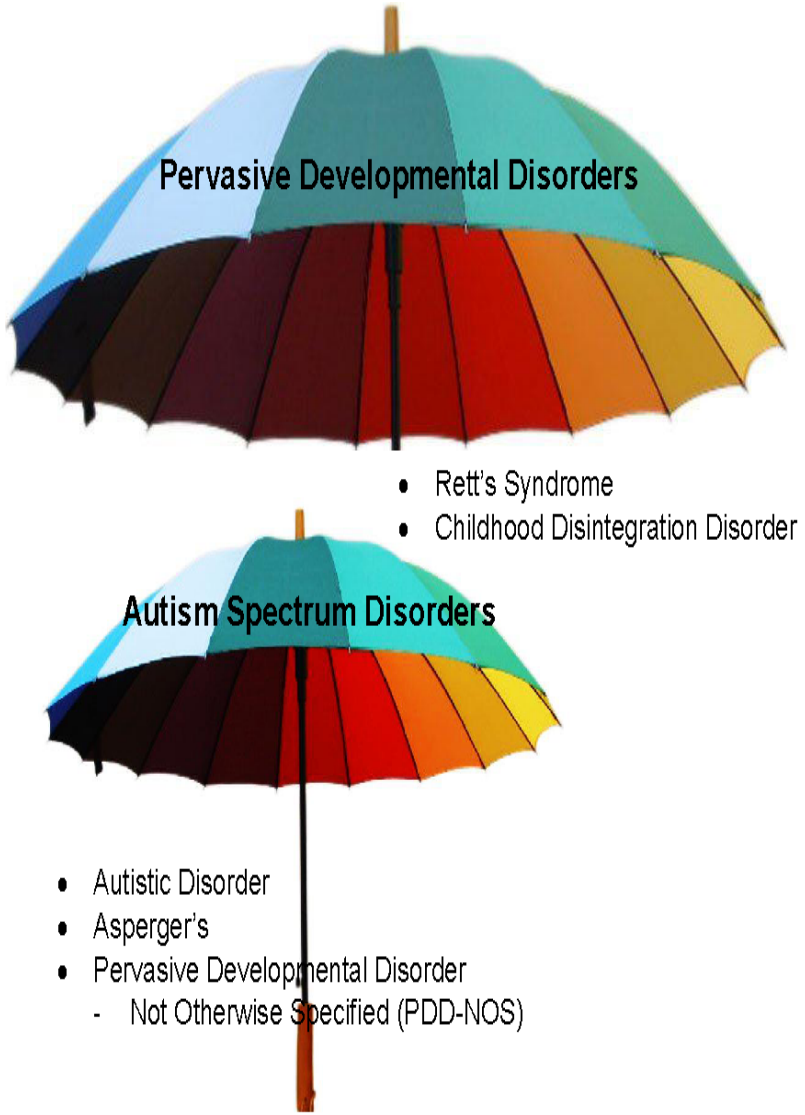


Ruchit Shah

Elly Farnell

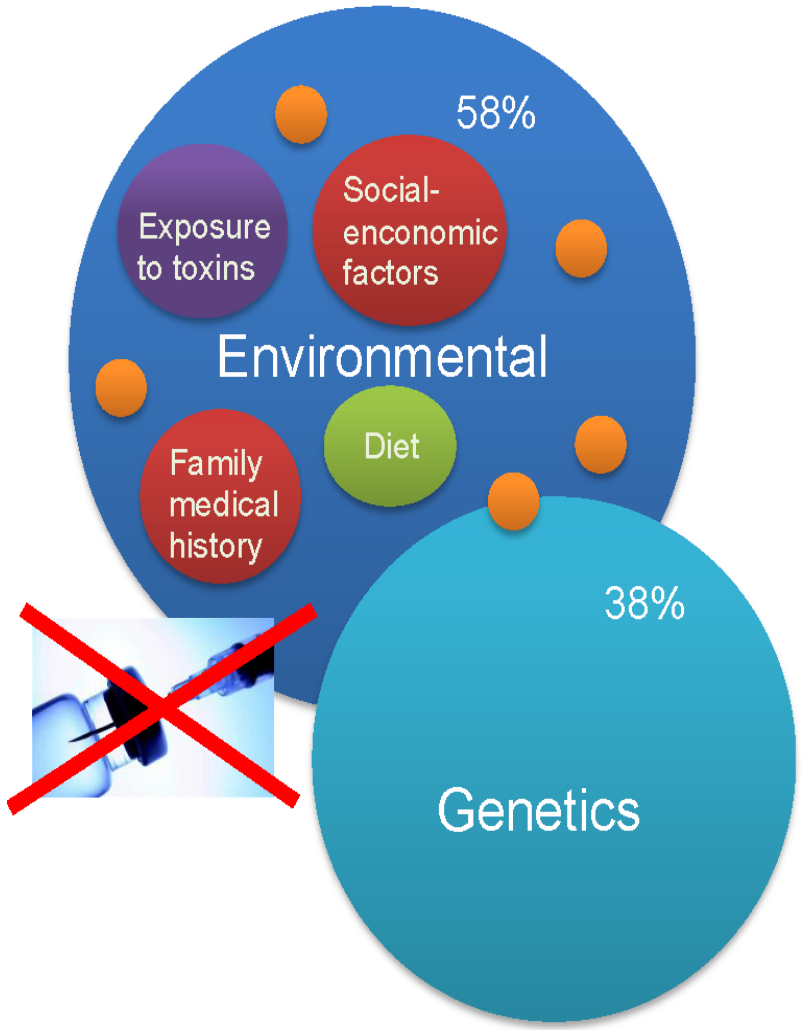
What is ASD?

- First identified in 1943 by Leo Kanner.
- The May 2013 publication of the DSM-5 diagnostic manual merged all autism disorders into one umbrella diagnosis of ASD.
- Autism is a neurodevelopmental disorder with 3 defining areas of deficit:
  1. Social reciprocity
  2. Communication
  3. Restricted, repetitive patterns of behaviors, interests, or activities.
- Symptoms are developed by 36 months of age.

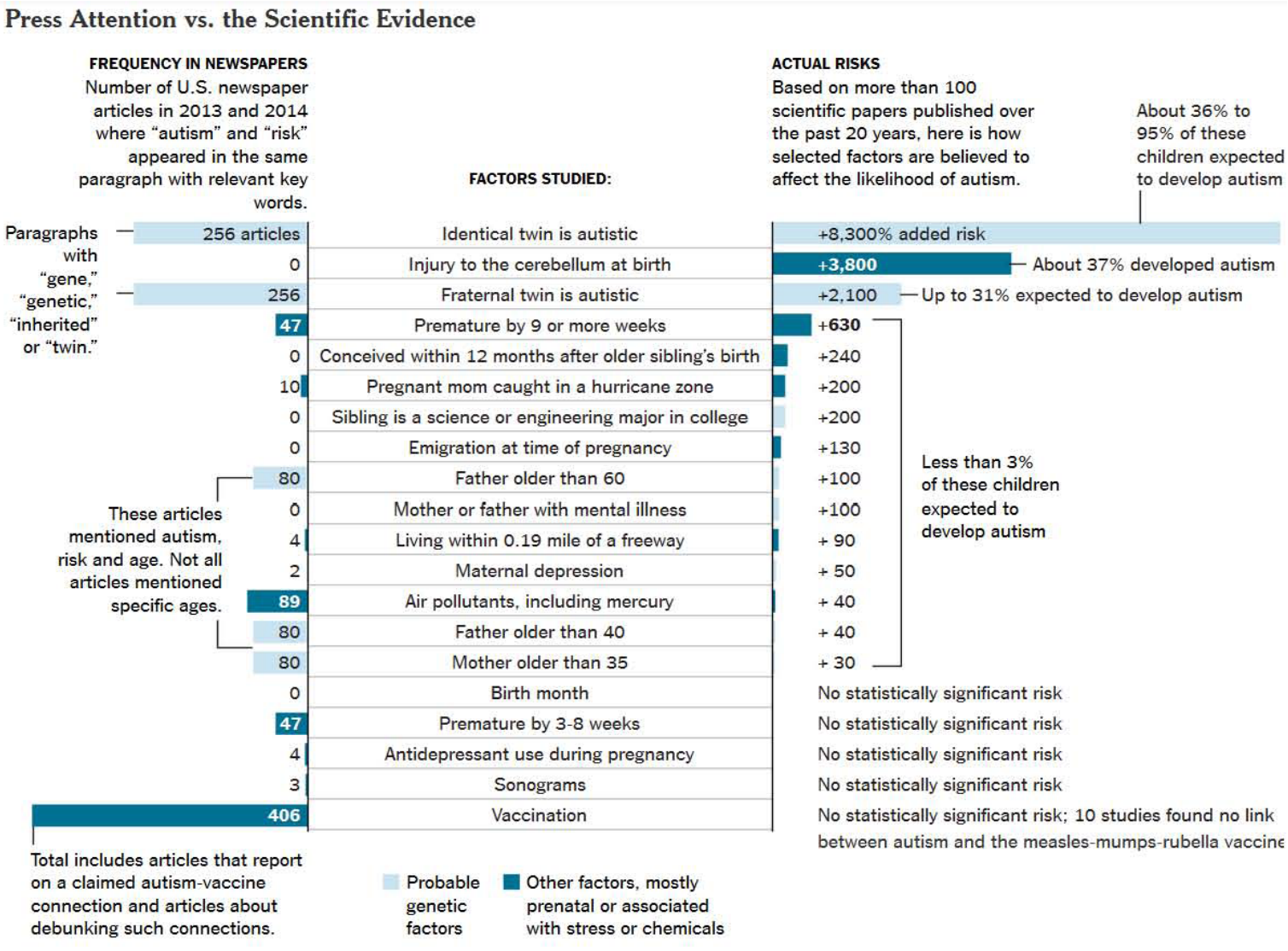


Causes

- The causes of autism are diverse: genetic and non-inherited factors or exposures.
  - **Genetic:** In identical twins, if one has ASD, the other twin also has ASD in nearly 8 out of 10 cases.
  - **Environmental:** Family medical history, demographic factors, exposure to toxins, complications during birth or pregnancy, diet, etc.
- Although no definitive answers yet, health experts are confident that there is little connection between vaccines and autism.



Press attention vs. the scientific evidence [1]



Statistics

- About 1 percent of the world population has ASD. (CDC, 2014)
- Percentage of U.S. population diagnosed with ASD (CDC, 2014):

$$\begin{cases} 1/5000 & \text{in 1975} \\ 1/88 & \text{in 2011} \\ 1/68 & \text{in 2013} \end{cases}$$

It is the fastest growing developmental disability in the U.S.

- Possible factors contributing to the increase:
  - Change in diagnosis criteria (accounts for $\approx 20\%$ of the overall $\uparrow$)
  - Trend towards younger age at diagnosis ($\approx 4\%$)
  - Broadening to include milder cases ($\approx 9.3\%$)
  - Older ages of mothers ($\approx 0.67\%$)

The remaining 66% deserves serious investigation.

Facts about ASD

Gender

$$\frac{\text{Boys}}{\text{girls}} = \frac{5}{1}$$

Risk

Couples with a child with autism are 9 times more likely to have another child with autism.

Diagnosis

- A standard two-stage screening process is currently in practice (for children at 18 and 24 months of age.).
- A diagnosis is usually made when a child is 3 to 4 years of age or older.
- EEG brain scans may detect signs of ASD in 2-year-olds [2].

Treatment

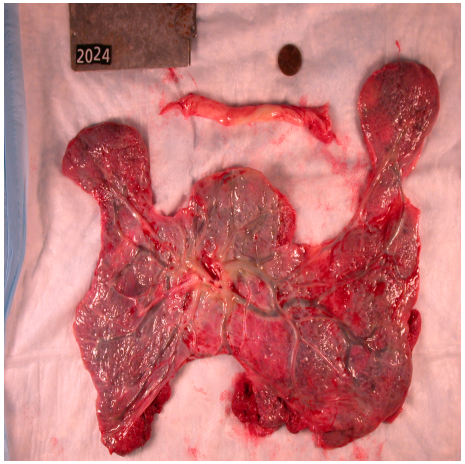
- There is no proven cure yet for ASD.
- The brain is most responsive to treatment in the first year of life.
- Early intervention (e.g., with intensive Early Start Denver Model (ESDM) that uses techniques of **Applied Behavioral Analysis**) is associated with normalized brain activities in young children with ASD (e.g., improved social and communication skills.) [3].
- But, since a diagnose of ASD is usually not made until the child is 3 or 4 years old, **the best opportunities for intervention have already been lost then**.

We are in great need to discover a reliable biomarker in assessing prenatal/neonatal ASD risk. So, why not consider the gestational origin of life — placenta?

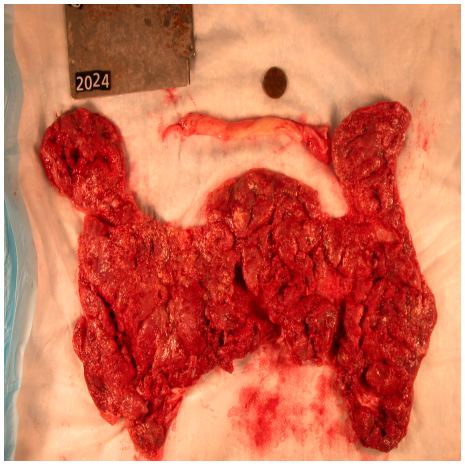
What is placenta?

- Nutrients, wastes, and gases are exchanged between the mother's and the baby's blood in the placenta.
- An analysis of the placenta may help to predict risks for certain diseases that develop in the womb such as diabetes, autism, and heart disease.
- For centuries the placenta has received ceremonial handling by many cultures around the world. (e.g., in China, placenta is considered as a rich source of nutrients and can be added to the diet to increase a person's energy and vitality.)

fetal side



maternal side



Why study placenta?

- In western medicine the human placenta is usually regarded as nothing more than human waste.
- In fact, only 10-15% of the placentas are analyzed, usually after pregnancy complications or a newborn's death.
- Altered patterns of angiogenesis $\Leftrightarrow$ variation in mature vascular network structures $\Leftrightarrow$ functional alterations of many viscera (e.g., lung, kidney, and pancreas).
- The gene families that control branching morphogenesis are shared between those permanent viscera and the temporary fetal organ – placenta.
- Placenta, hence, provides unique insights into the effects of genes and/or environment (or both) on key mechanisms required for conceptus development, including fetal origins of disease from hypertension to diabetes and autism.

How to study placenta?

Can you tell which placenta is more likely to have supported a healthy baby and which one is less likely so?

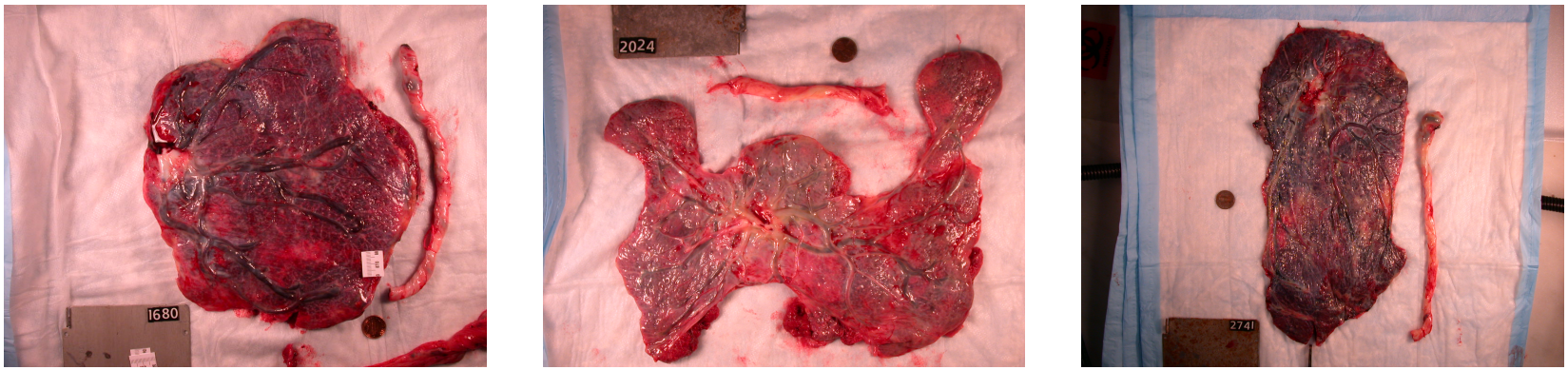
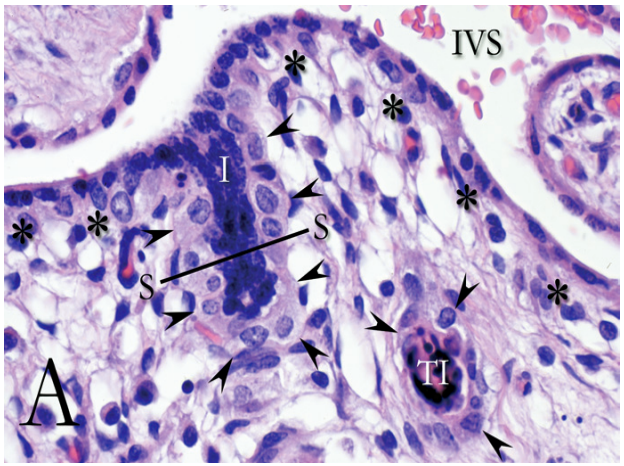


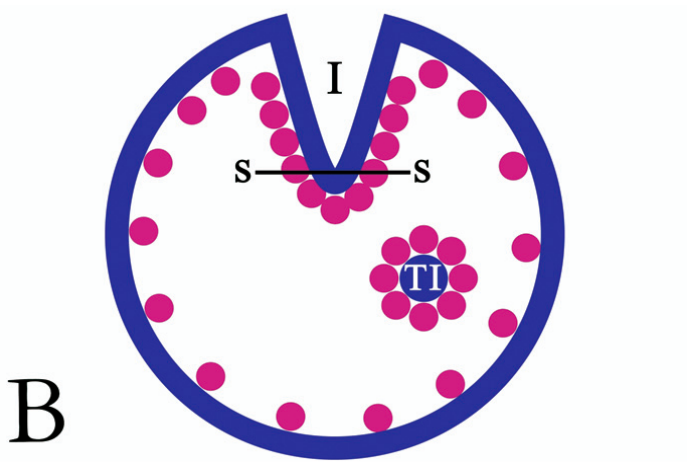
Figure: Sample digital placenta images in the UNC data set provided by Placental Analytics.

Placenta & ASD: Trophoblast inclusions [4]

- Placentas from at-risk pregnancies (in which the families already had 1 or more children with ASD) were 8 times more likely to have two or more TIs than placentas from uncomplicated pregnancies.
- The more trophoblast inclusions you have, the more severe the abnormality.



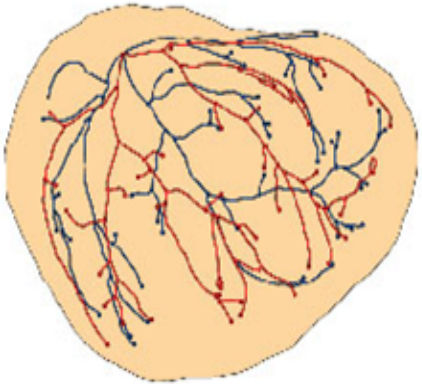
histology



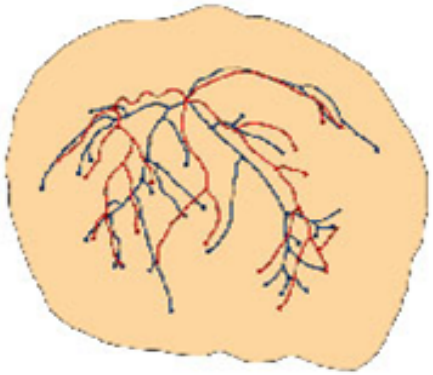
villus cross-section

Figure: [5] **(A)** histologic section of a placental villus which exhibits a trophoblast inclusion (TI). **(B)** Diagram of a villus cross-section showing the outer syncytiotrophoblast layer (blue line) and inner cytotrophoblast layer (pink circles) with a trophoblast inclusion (TI).

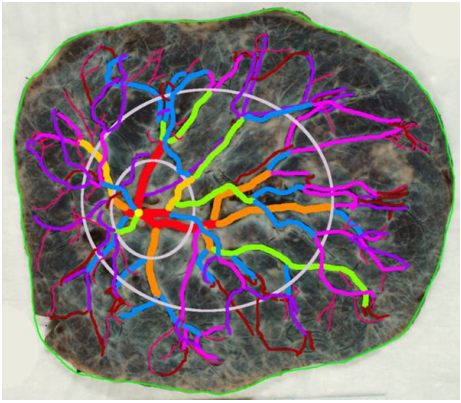
Placenta & ASD: Angiogenesis [6]



mean of low-risk



mean of high-risk



manually traced

Placental angiogenesis and ASD	Low-ASD risk		High-ASD risk		Significance
	Arterial	Venous	Arterial	Venous	
# branch generations	8.86±1.69	9.24±2.11	7.65±1.72	8.07±1.76	high-risk group has fewer branch generations
# branch pts in network	29.94±11.13	32.86±11.92	21.67±8.96	26.91±9.45	high-risk group has fewer branch points
mean dist of vessel endpts to disk edge	2.24±.50	2.34±0.51	2.78±.63	2.51±0.55	placenta from high-risk group fails to extend as close to the chorionic perimeter as low-risk group does.

Significant implications: Angiogenesis

These methods open doors to

1. prenatal/neonatal ASD **risk assessment** and
2. **early detection and intervention** for newborns with elevated risks for ASD,

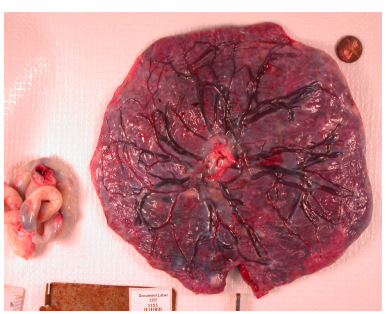
given that we have a reliable method to **compute** **vessel features** that are proxies for predicting health risks.

Research challenges

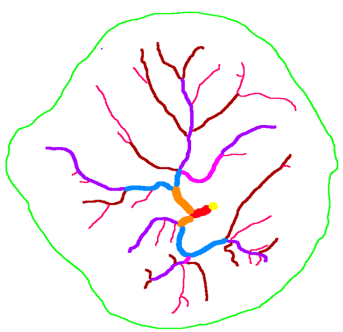
- Data set sizes and time it takes to make a diagnosis.

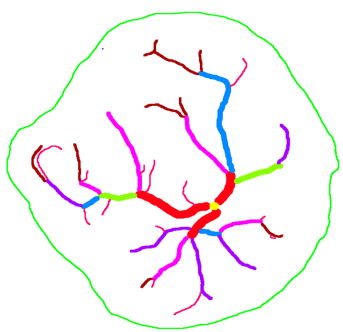
Data set	# of cases used	Data description/purpose
MARBLE (Markers of Austism Risk in Babies - Learning Early Signs)	117	cohort of families who have one or more previous biological children with ASD
EARLI (Early Autism Risk Longitudinal Investigation)	46 traced placentas (from 150 available ones)	self-enrolled group of mothers of children with autism at the start of another pregnancy. The newborn child's development is examined through three years of age.
NCS (National Children's Study)	78 traced placentas (from 250 available ones)	NCS examines the effects of the environment (e.g., air, water, diet, sound, family dynamics, community and cultural influences, and genetics on the growth, development, and health of children across the U.S.), following them from before birth until 21 years of age.

- PCSVN extraction is currently done manually, making large-scale studies and real-time diagnosis intractable.



$\longrightarrow$ human





Research questions

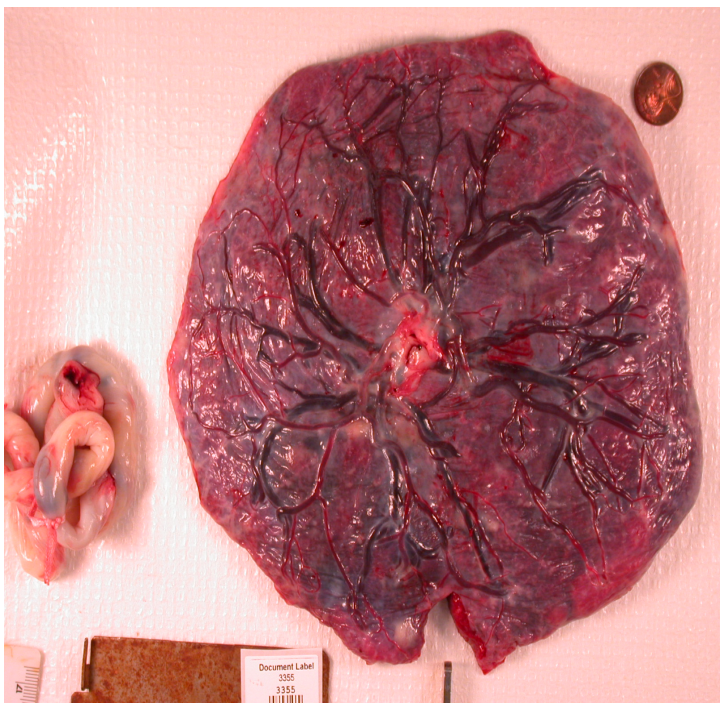
A What are these powerful vessel features?

- Currently investigating this
- Model selection (statisticians) & physical interpretation (doctors) are needed
- $>$ 100 features computed on NCS & EARLI are available

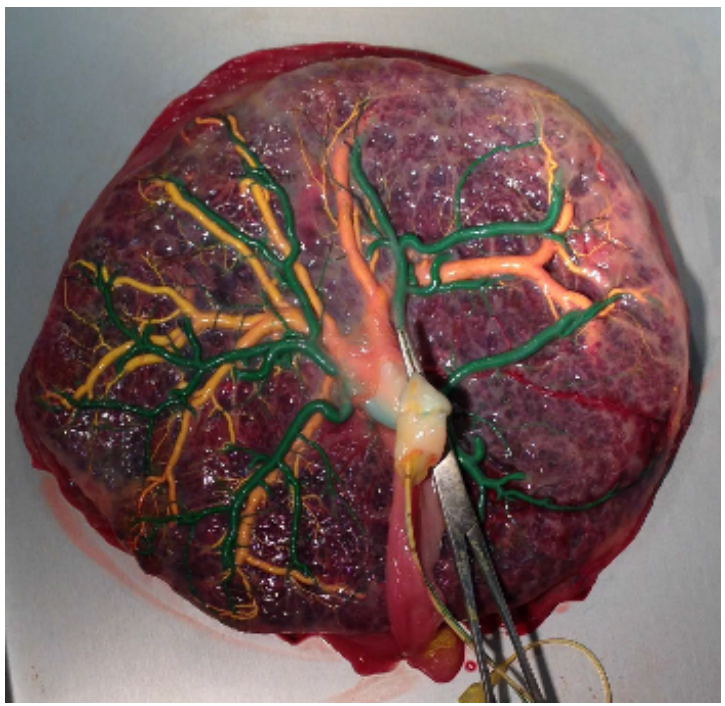
Area	surface area of placenta in cm^2
Perimeter	perimeter of placenta in cm
Compactness	4*Pi*Area/(Perimeter)^2
Sigma_UCI	std. deviation of radii w.r.to mean radius obtained from insertion pt. of disc
Rmean	mean of the radii obtained from insertion pt. of disc in cm
RmeanN	Rmean/sqrt(Area)
UCI_to_Perim	Min distance of the UCI to the Perimeter in cm
A_SurfaceArea	surface area of the arterial network as determined from the traced arteries on the 2D fixed fetal surface image
A_VesselToDiscPercent	(No. of pixels of arterial network/No. of pixels in whole disc)*100
A_NumGenerations	maximum number of times an artery branches + 1 (first generation is artery originating from uci, second generation is first branch,...)
A_NumCordBranches	number of arteries that originate from the uci
A_NumBranchPoints	total number of arterial branch points (counts the uci as a branch point)
A_NumEndPoints	total number of arterial end points
A_ArcLength	arc length of the arterial network
A_Volume	volume of the arterial network
A_MeanThickness	mean thickness of the arterial network
A_StdThickness	standard deviation of the thickness of the arterial network
A_MurrayExponent	Exponent that minimizes [(mother)^exp - (d1^exp + d2^exp)]
A_MurrayL1FitError	Mean error in terms of how far [(mother)^exp - (d1^exp + d2^exp)] is from 0
A_MeanDistToPerim	average distance between point on artery and point on perimeter

Research questions

- **What kind of placental surface image should be used for vessel extraction?**
  - Preliminary results available on UNC unfiltered data [7, 8]
  - Currently exploring paint-injected data [9]



vs.



Research goal - Question B

To answer Question B, we need to

1. first develop an **automated** program to extract Placental Chorionic Surface Vascular Networks (PCSVNs).

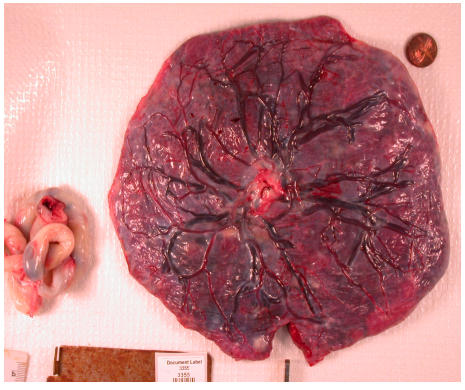
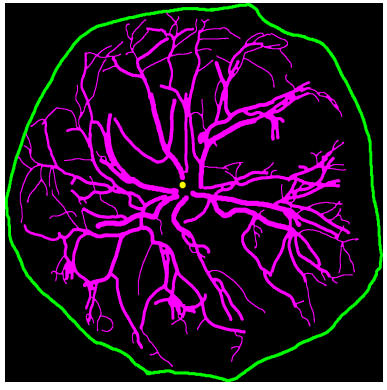


image captured

automatically



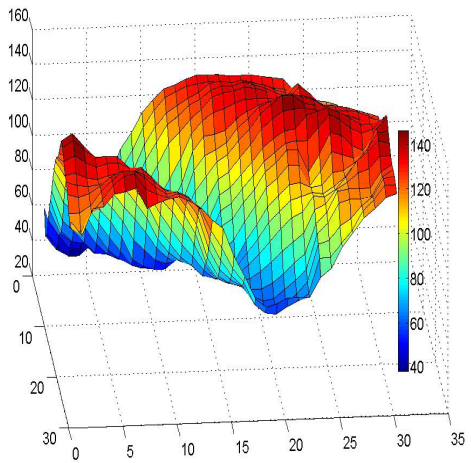
desired output

2. then assess the quality of extraction algorithms for placental features such as surface area, number of branching generations, distribution of distance from endpoints to perimeter, arc length, mean vessel width, variability in vessel width, number of branch points, etc.

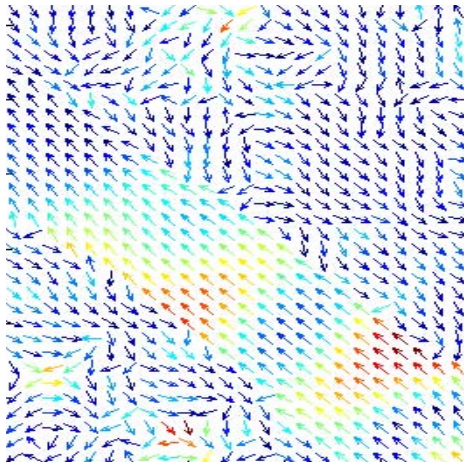
Result - Question B [7]

- A **multiscale** filtering process that is based on images' 2nd-order feature is used to highlight **locally curvilinear** structures and minimize surrounding non-vessel noise.

a vessel



intensity surface



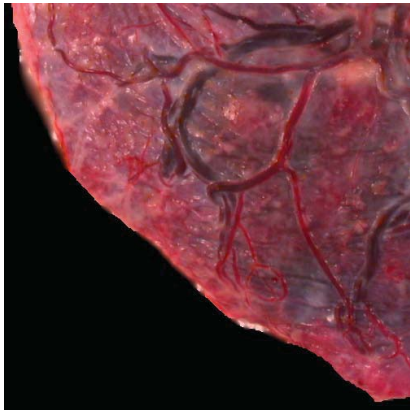
$\mathbf{v}_1$ of $\mathbf{H}$

- The proposed method performs superior than all existing competitor's work.

Result - Question B [7]

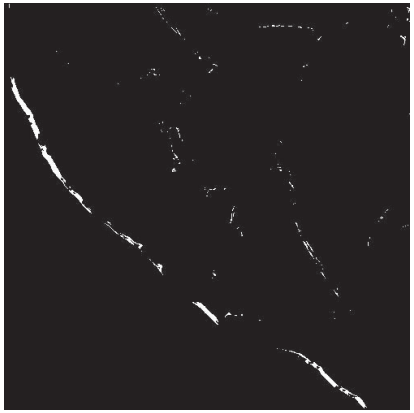
Many issues such as **tissue dampness**, **arteries cross over veins**, and **variable contrast** lead to fragmented extraction.

64-bit laptop w/Windows
Intel(R) Core(TM) i7-3770 @ 3.4GHz CPU, 8GB RAM
implemented in MATLAB
$\sigma \in \{4,6\}, \beta = 0.5, c = 15$
$\omega = 5, \ell = 14, \alpha = 0.04$
NN = 36.68s, MVE = 0.92s
C.L. Enhancement = 4.44s



(a) UNC #3355

(b) hand traced



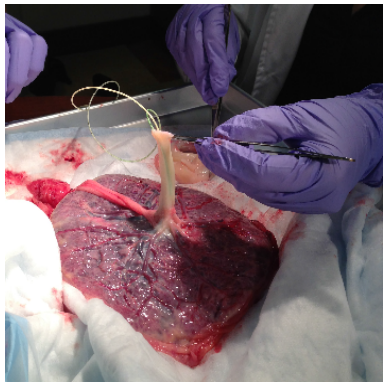
(c) neural network

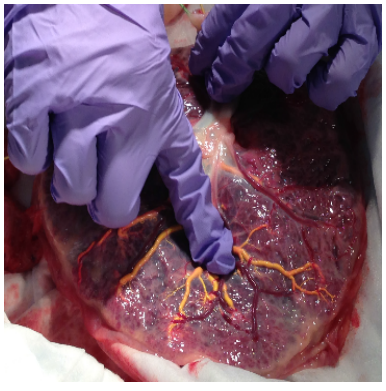
(d) multiscale

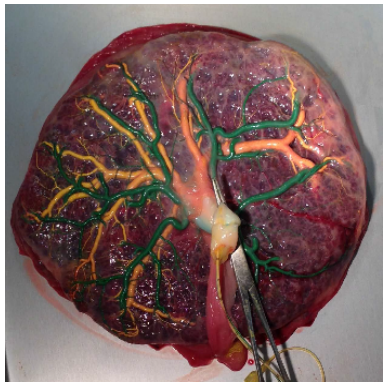
(e) [7]

Result - Question B [9]

Consider alternative imaging strategies — **dye injection**


(a)


(b)


(c)

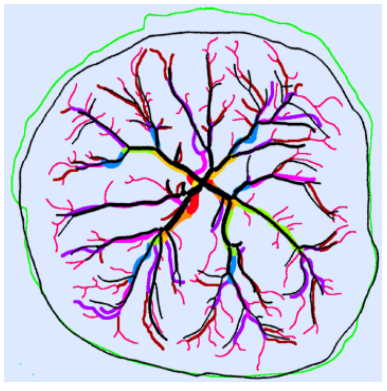
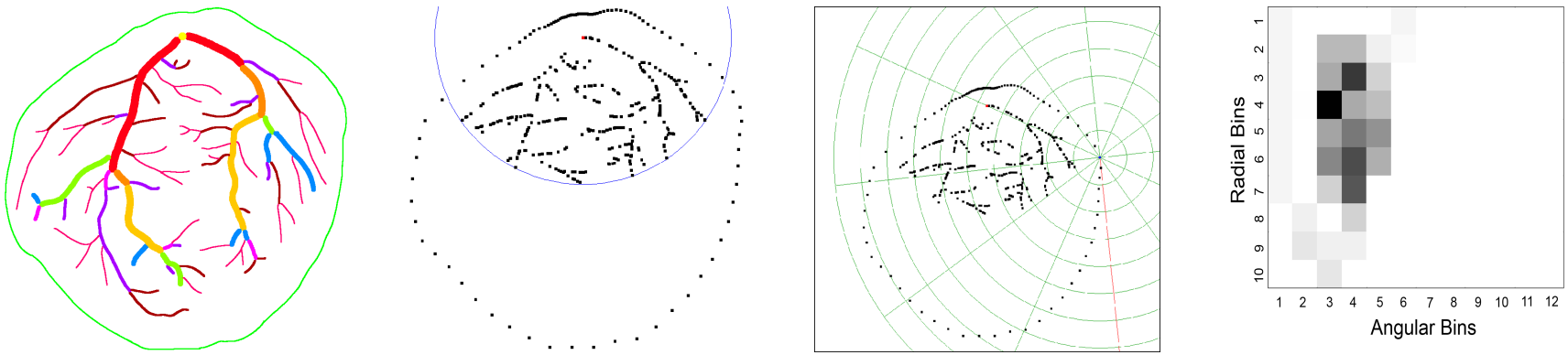

(d)

Figure: (a) A formalin-fixed placenta undergoing dye injection. (b) Dye is massaged through the vessels. (c) A dye-injected PCSVN. (d) A superposition of hand-traced PCSVNs before (black) and after injection (color).

Problem: changes induced by the injection process.

Result - Question B [9]

Preliminary results showed that using an angular-based shape descriptor, **distinguishing features of placental PCSVN are preserved during paint-injection**.



(a) (b) (c) (d)

Figure: (a) Tracing of un-injected placenta; (b) sample points from (a), blue arc illustrates a disk of radius 300 centered at the insertion point (red); (c) visual representation of polar mesh with red line segment denoting the positive x-axis; (d) histogram for the sample point in (c).

Summary

1. Understanding the causes for ASD is of national urgency.
2. Early intervention is the best treatment plan.
3. Placenta, as a diary of gestational life, should be carefully studied.
4. Interdisciplinary collaboration can greatly contribute to the overall understanding of the problem.

THANK YOU

References

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