Why We *Still* Need A Human Placenta Project AND Continued Placenta Research To Support Our Understanding Of DOHaD

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Eunice Kennedy Shriver National Institute
of Child Health and Human Development

David Weinberg

Note: This presentation includes presenter notes.

Disclosures

No conflicts to disclose

The views presented are mine

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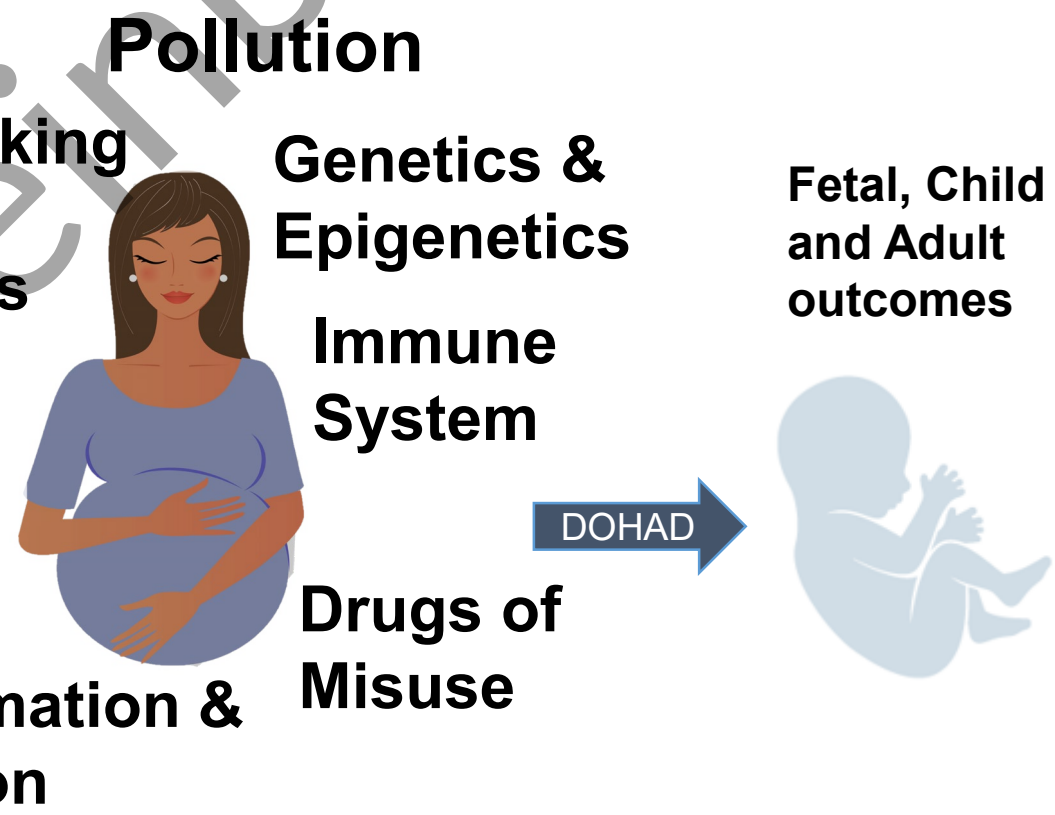
Mom's Environment Matters

The placenta has many critical functions, including:

- **Bringing nutrients and oxygen to the fetus**
- **Removing harmful waste**
- **Producing hormones to support fetal development**
- **Providing Immune Protection**
- **Providing a Physical Barrier to Mom's Blood**

Placenta dysfunction can lead to adverse pregnancy or developmental outcomes, such as **Preeclampsia**, **Preterm Birth. Growth Restriction**, etc., and impact long term child and adult health



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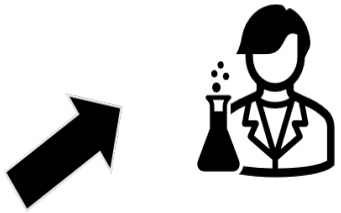
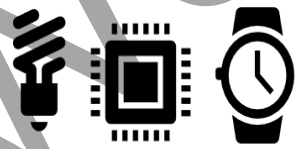
2014 - A Human Placenta Project to Move the Field

Understand *human* placenta development and function

INSIGHT



>$91 Million to date



INNOVATION

Develop novel tools for safe, non-invasive, real-time assessment across pregnancy

INTERVENTION

Generate new insights that lead to **novel diagnostics and treatment**

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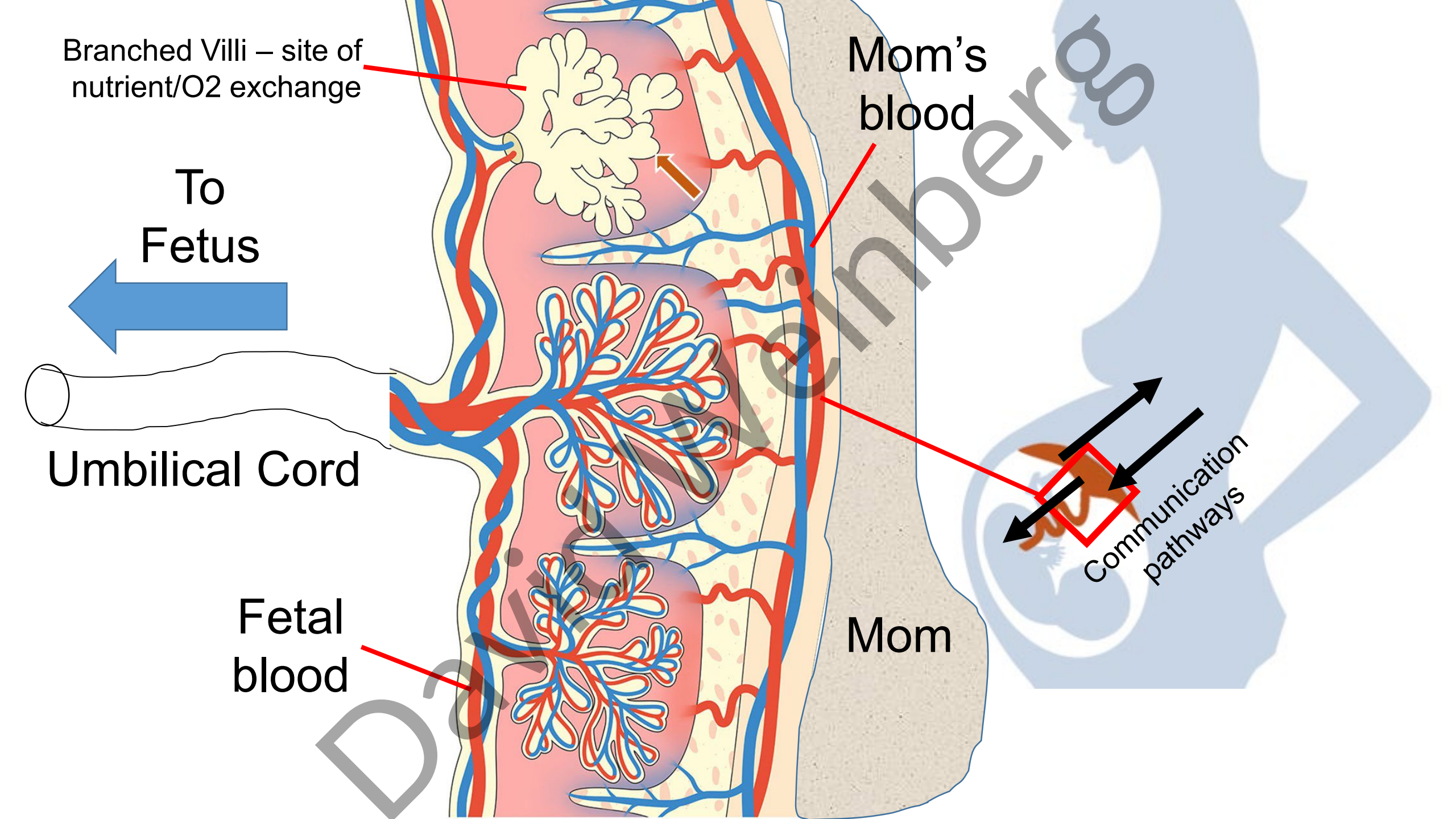
Branched Villi – site of nutrient/O2 exchange
To Fetus
Umbilical Cord
Fetal blood
Mom's blood
Mom
Communication pathways

Outcomes of the Human Placenta Project

Fully **automated**, real-time 3D **ultrasound** segmentation to estimate first trimester placental volume using deep learning. Looney P, Stevenson GN, Nicolaides KH, Plasencia W, Molloholli M, Natsis S, **Collins SL.** JCI Insight. 2018 Jun 7;3(11):e120178

Quantitative longitudinal T2* mapping for assessing placental function and association with adverse pregnancy outcomes across gestation. Schabel MC, Roberts VHJ, Gibbins KJ, Rincon M, Gaffney JE, Streblow AD, Wright AM, Lo JO, Park B, Kroenke CD, Szczotka K, Blue NR, Page JM, Harvey K, Varner MW, Silver RM, Frias AE. PLoS One. 2022 Jul 19;17(7):e0270360

Non-invasive monitoring of blood oxygenation in human **placentas** via concurrent diffuse optical spectroscopy and **ultrasound imaging**. Wang L, Cochran JM, Ko T, Baker WB, Abramson K, He L, Busch DR, Kavuri V, Linn RL, Parry S, Yodh AG, **Schwartz N.** Nat Biomed Eng. 2022 Sep;6(9):1017-1030

Trophoblastic extracellular vesicles and viruses: Friends or foes? Ouyang Y, Mouillet JF, Sorkin A, Sadovsky Y. Am J Reprod Immunol. 2021 Feb;85(2):e13345

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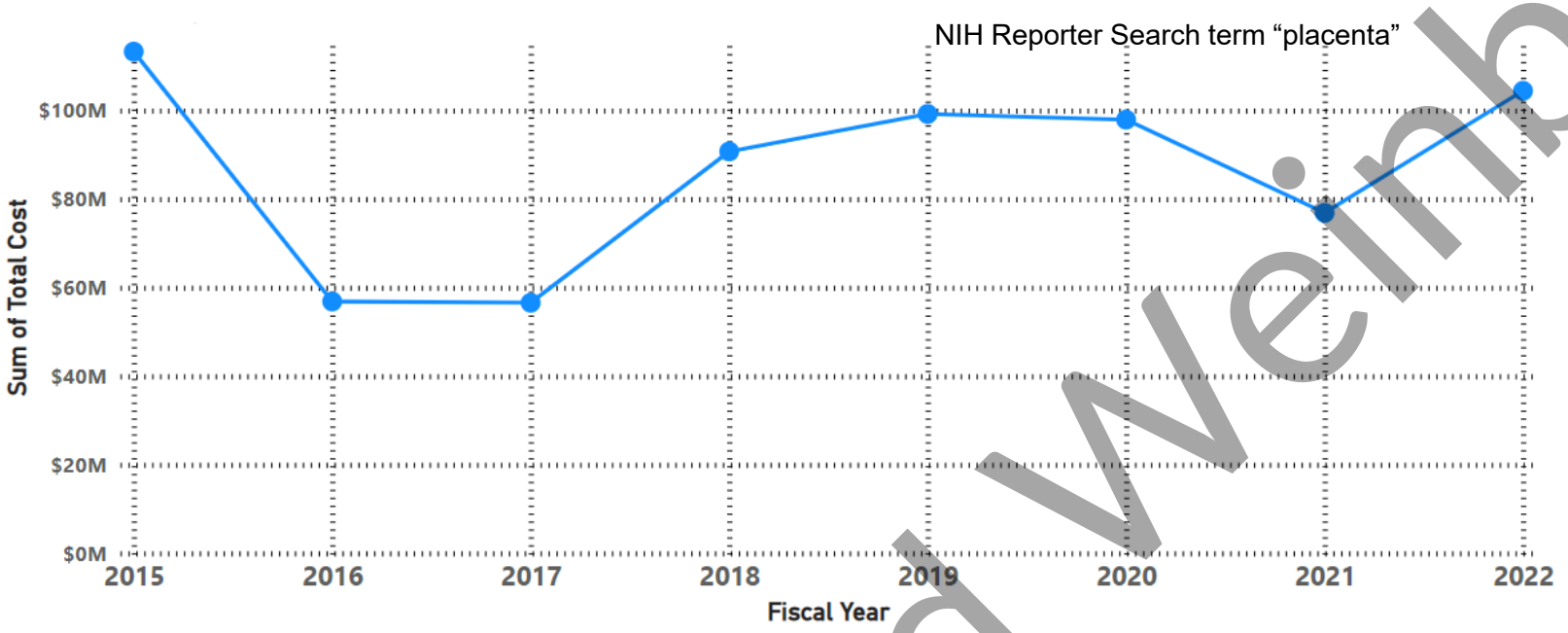
NIH Funding of Placenta Research: more than $695M from 2015-2022



Fiscal Year	Sum of Total Cost
2022	$104,439,138
2021	$76,875,255
2020	$97,925,708
2019	$99,211,439
2018	$90,745,322
2017	$56,571,203
2016	$56,856,352
2015	$113,291,814
TOTAL	$695,916,231

Placenta Research Remains and NICHD Priority

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NIH Funding Opportunities That Demonstrate Commitment to DOHaD

2023: HEAL Initiative: Opioid Exposure and Effects on Placenta Function, Brain Development, and Neurodevelopmental Outcomes

RFA Goal:

Address the gap in our understanding of the **placenta's role in adverse fetal neurodevelopment and child neurodevelopmental outcomes** due to prenatal opioid exposure using human studies or animal models

Expected impact:

- **Mechanistic insights** that point to new biologic pathways and research directions
- **Novel biomarkers** for research and diagnostics

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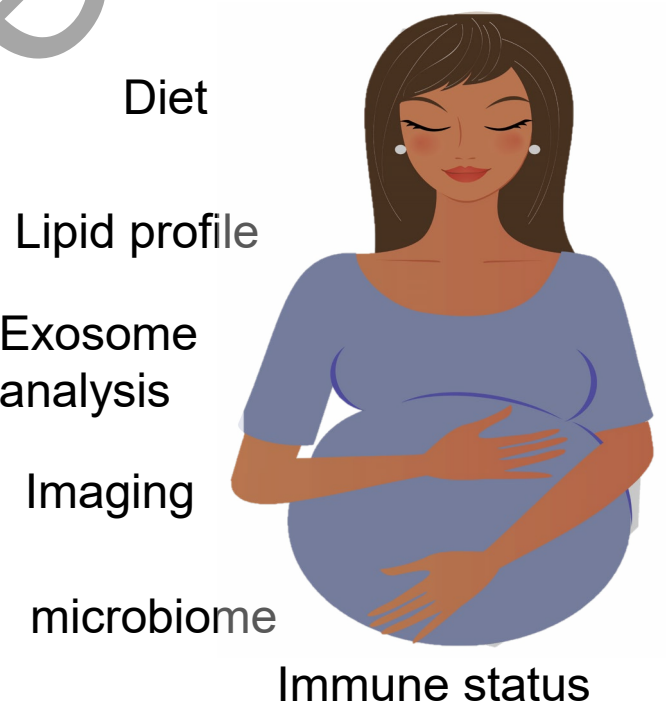
Many Challenges Remain

- There may be many paths to the symptoms that present themselves
- Signals may be indications of normal compensation, not pathology
- Time/cost/risk-benefit issues related to increased testing (imperfect information)
  - Clinical benefits unclear
- Associations often clearer in the aggregate
- New technologies lack rigorous clinical confirmation
  - Disparities may prevent equal access
- Lack of basic ground truth – range of variation of ‘normal’ is unknown

What is possible vs what is expedient



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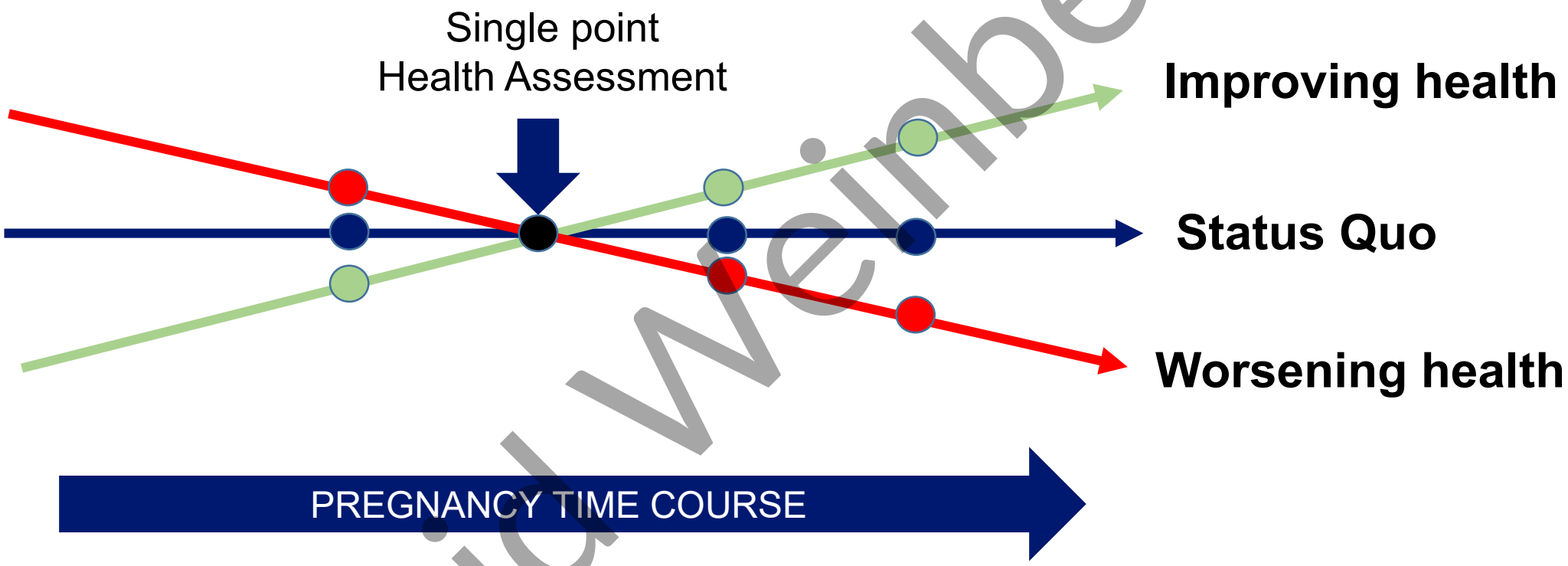
Longitudinal Assessment is Critical For Pregnancy Care



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Potential For Innovation seen in other areas of human health

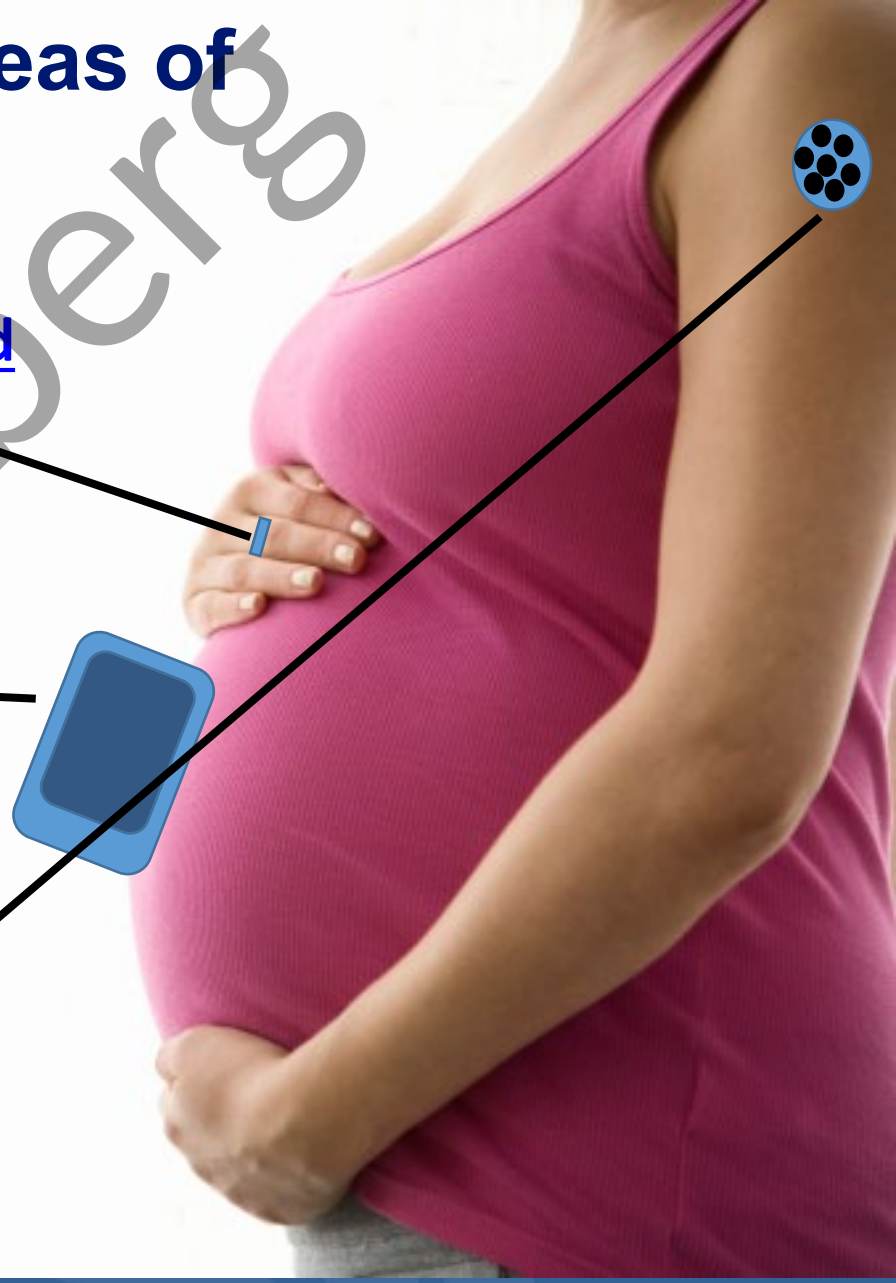
Multi-Night Validation of a Sleep Tracking Ring in Adolescents Compared with a Research Actigraph and Polysomnography.

Chee NIYN, Ghorbani S, Golkashani HA, Leong RLF, Ong JL, Chee MWL.Nat Sci Sleep. 2021 Feb 15;13:177-190

Point-of-care ultrasound assessment with handheld ultrasound device attached to cell phone

.Sauza-Sosa JC, Arratia-Carlin K, Fernandez-Tapia J.J Clin Ultrasound. 2022 Feb;50(2):284-285

An epidermal patch for the simultaneous monitoring of haemodynamic and metabolic biomarkers. Sempionatto JR, Lin M, Yin L, De la Paz E, Pei K, Sonsa-Ard T, de Loyola Silva AN, Khorshed AA, Zhang F, Tostado N, Xu S, Wang J.Nat Biomed Eng. 2021 Jul;5(7):737-748



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Potential For Innovation seen in other areas of human health

Clinical validity of saliva and novel technology for cancer detection

.Kaczor-Urbanowicz KE, Wei F, Rao SL, Kim J, Shin H, Cheng J, Tu M, Wong DTW, Kim Y.Biochim Biophys Acta Rev Cancer. 2019 Aug;1872(1):49-59

Toilet-based continuous health monitoring using urine.Tasoglu S.Nat Rev Urol. 2022 Apr;19(4):219-230

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New Models

Organ-on-a-Chip

Organ-on-a-chip for perinatal biology experiments.

Menon R, Richardson L.Placenta Reprod Med. 2022 Jul 6;1:9

Development of a novel dual reproductive organ on a chip: recapitulating bidirectional endocrine crosstalk between the uterine endometrium and the ovary.

Park SR, Kim SR, Lee JW, Park CH, Yu WJ, Lee SJ, Chon SJ, Lee DH, Hong IS.Biofabrication. 2020 Oct 16;13(1)`

Organoids

Stem-cell-derived trophoblast organoids model human placental development and susceptibility to emerging pathogens.

Karvas RM, Khan SA, Verma S, Yin Y, Kulkarni D, Dong C, Park KM, Chew B, Sane E, Fischer LA, Kumar D, Ma L, Boon ACM, Dietmann S, Mysorekar IU, Theunissen TW.Cell Stem Cell. 2022 May 5;29(5):810-825

Trophoblast organoids as a model for maternal-fetal interactions during human placentation.

Turco MY, Gardner L, Kay RG, Hamilton RS, Prater M, Hollinshead MS, McWhinnie A, Esposito L, Fernando R, Skelton H, Reimann F, Gribble FM, Sharkey A, Marsh SGE, O'Rahilly S, Hemberger M, Burton GJ, Moffett A.Nature. 2018 Dec;564(7735):263-267

Stem Cells

Modeling preeclampsia using human induced pluripotent stem cells.

Horii M, Morey R, Bui T, Touma O, Nelson KK, Cho HY, Rishik H, Laurent LC, Parast MM.Sci Rep. 2021 Mar 15;11(1):5877

Derivation of Human Trophoblast Stem Cells.

Okae H, Toh H, Sato T, Hiura H, Takahashi S, Shirane K, Kabayama Y, Suyama M, Sasaki H, Arima T.Cell Stem Cell. 2018 Jan 4;22(1):50-63.e6. doi: 10.1016/j.stem.2017.11.004. Epub 2017 Dec 14.

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Interventions Are Being Developed

Pathogenesis of Preeclampsia and Therapeutic Approaches Targeting the Placenta.

Jena MK, Sharma NR, Petitt M, Maulik D, Nayak NR.Biomolecules. 2020 Jun 24;10(6):953

Targeting the Dysfunctional Placenta to Improve Pregnancy Outcomes Based on Lessons Learned in Cancer.

Wilson RL, Jones HN.Clin Ther. 2021 Feb;43(2):246-264

Novel Technologies for Target Delivery of Therapeutics to the Placenta during Pregnancy: A Review.

Pepe GJ, Albrecht ED.Genes (Basel). 2021 Aug 17;12(8):1255

Dynamic placenta-on-a-chip model for fetal risk assessment of nanoparticles intended to treat pregnancy-associated diseases.

Shojaei S, Ali MS, Suresh M, Upreti T, Mogourian V, Helewa M, Labouta HI.Biochim Biophys Acta Mol Basis Dis. 2021 Jul 1;1867(7):166131

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The Future of Placenta Research Will Depend upon the Next Generation of Researchers

- **Will need:** clinicians, cell biologists, immunologists, microbiologists, data scientists, bioengineers, radiologists, vascular biologists, pharmacologists, pathologists, drug developers, and more…

- **Topics include:** modes of communication between mom, fetus and placenta; basic mechanisms of placenta development; mechanisms that underlie placenta dysfunction and potential targets for intervention; safe delivery vehicles for therapeutic agents; drug discovery for new therapeutics, validity of new models, regulation of nutrient transport and response to the environment; mechanisms underlying DOHAD in the face of environmental influences; regulation of drug transport across the placenta; biomarkers of placenta health across pregnancy; point of care technologies that may be used in low resource settings; the impact of stress on the maternal/fetal/placental ecosystem; the role of the microbiome; imprinting; paternal factors; impact of antiretroviral therapy, and more…

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There is plenty of room for new investigators!

Les Myatt

Kent Thornburg

HPP meeting at NIH

Terry Morgan!

Thank you!

Davis Members

Reference Material

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We Have NOT Solved the Problem of Adverse Pregnancy Outcomes

In the United States 2021

- 3,664,292 births
  - **Preterm: 10.49%**
  - **Low birthweight: 8.52%**

- Higher than in 2020 across race and ethnicity
- Worse for non-Hispanic Black mothers than non-Hispanic White mothers

- **Preeclampsia** >3% of all pregnancies (100,000 women per year)

https://www.cdc.gov/nchs/fastats/births.htm
https://www.cdc.gov/nchs/data/nvsr/nvsr72/nvsr72-01.pdf

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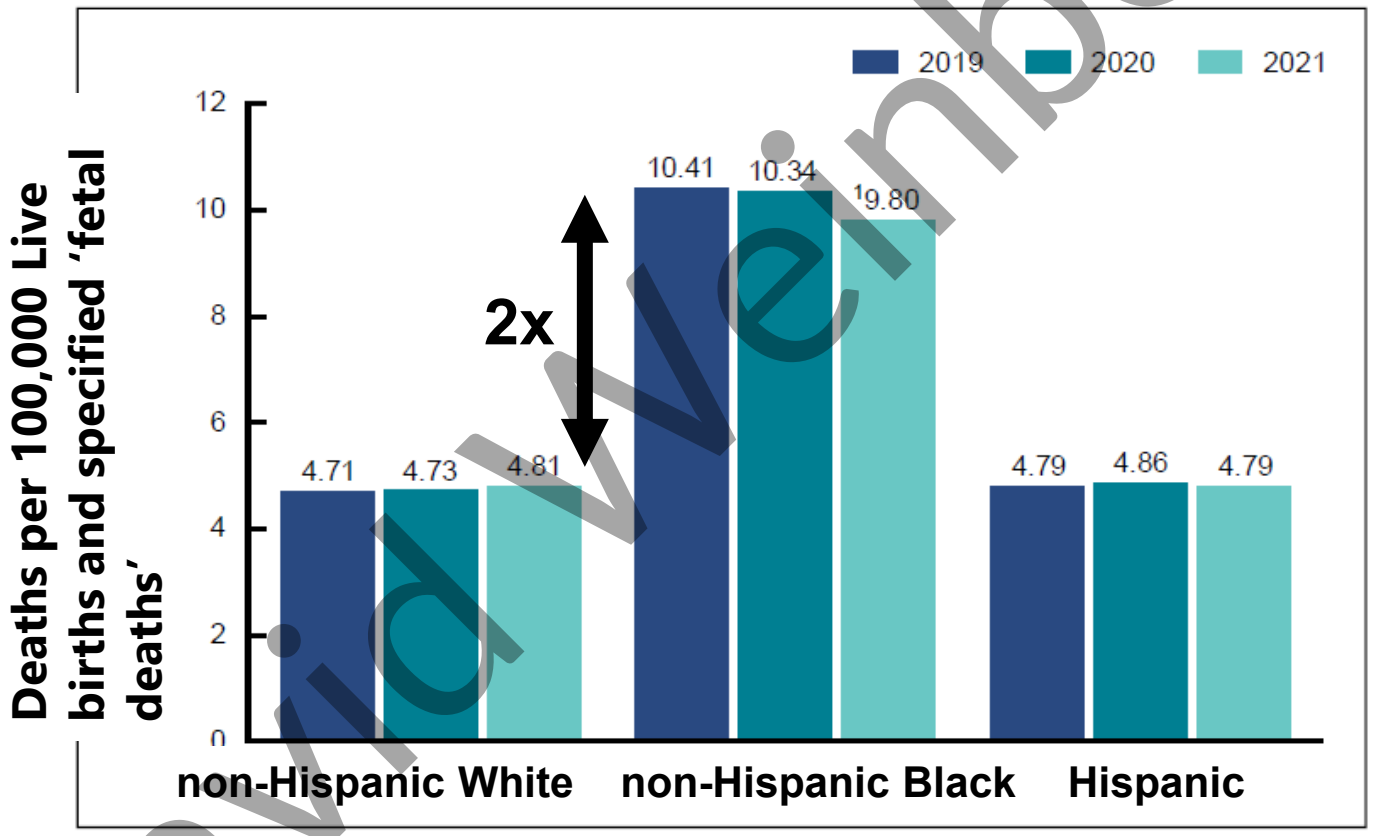
Fetal Mortality Has Not Decreased Substantially

Figure 2. Fetal mortality rates by race and ethnicity of mother: United States, 2005



[1]Significantly lower than 2020 ($p < 0.05$).
SOURCE: National Center for Health Statistics, National Vital Statistics System.

~400 annual deaths of non-Hispanic Black fetuses

https://www.cdc.gov/nchs/data/vsrr/vsrr026.pdf

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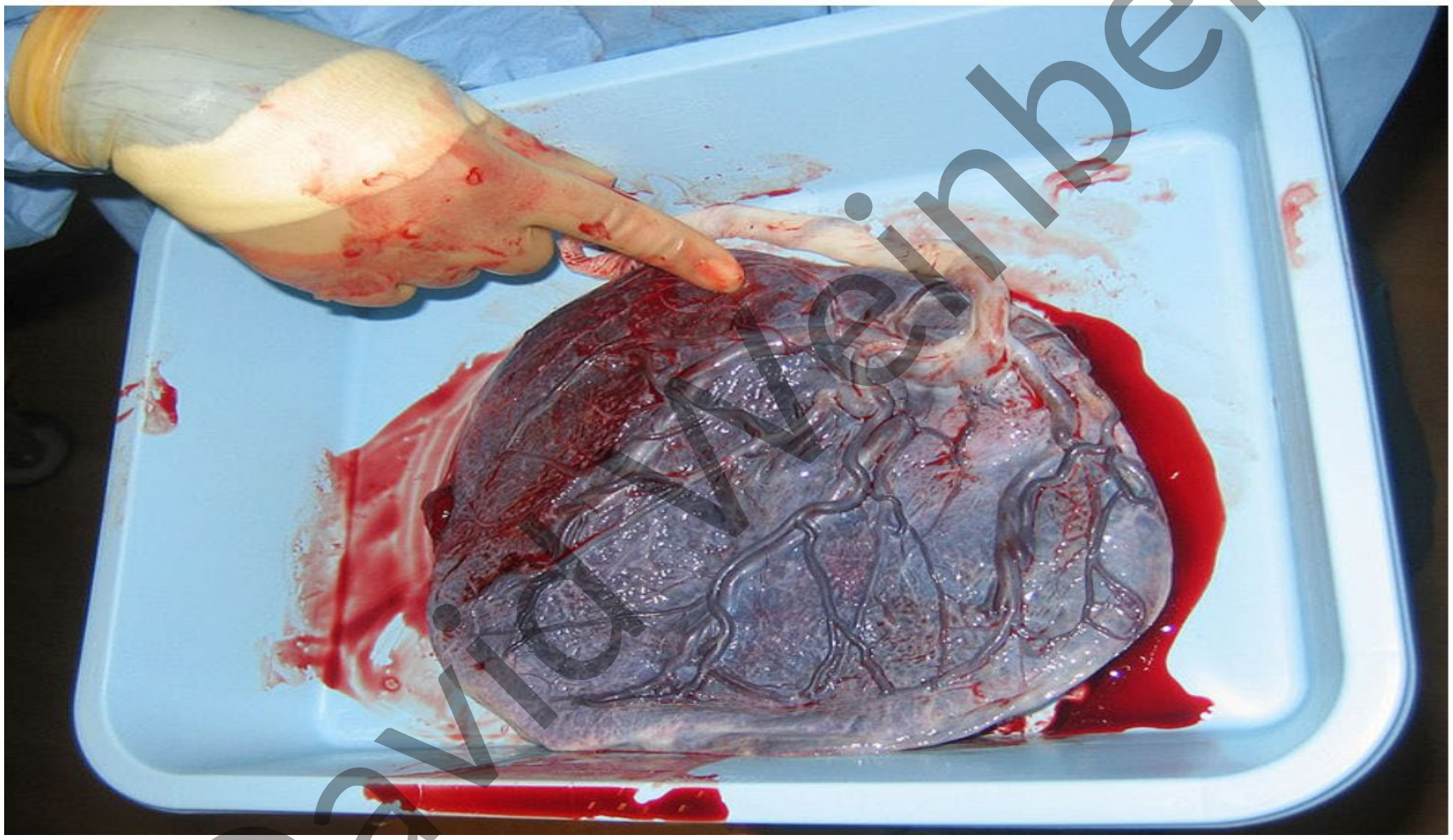
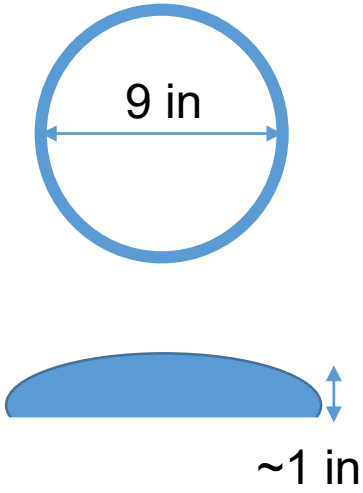
The Placenta As We Know It





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Adapting Technologies Already In Use in Pregnancy

- Blood Draws
- Imaging

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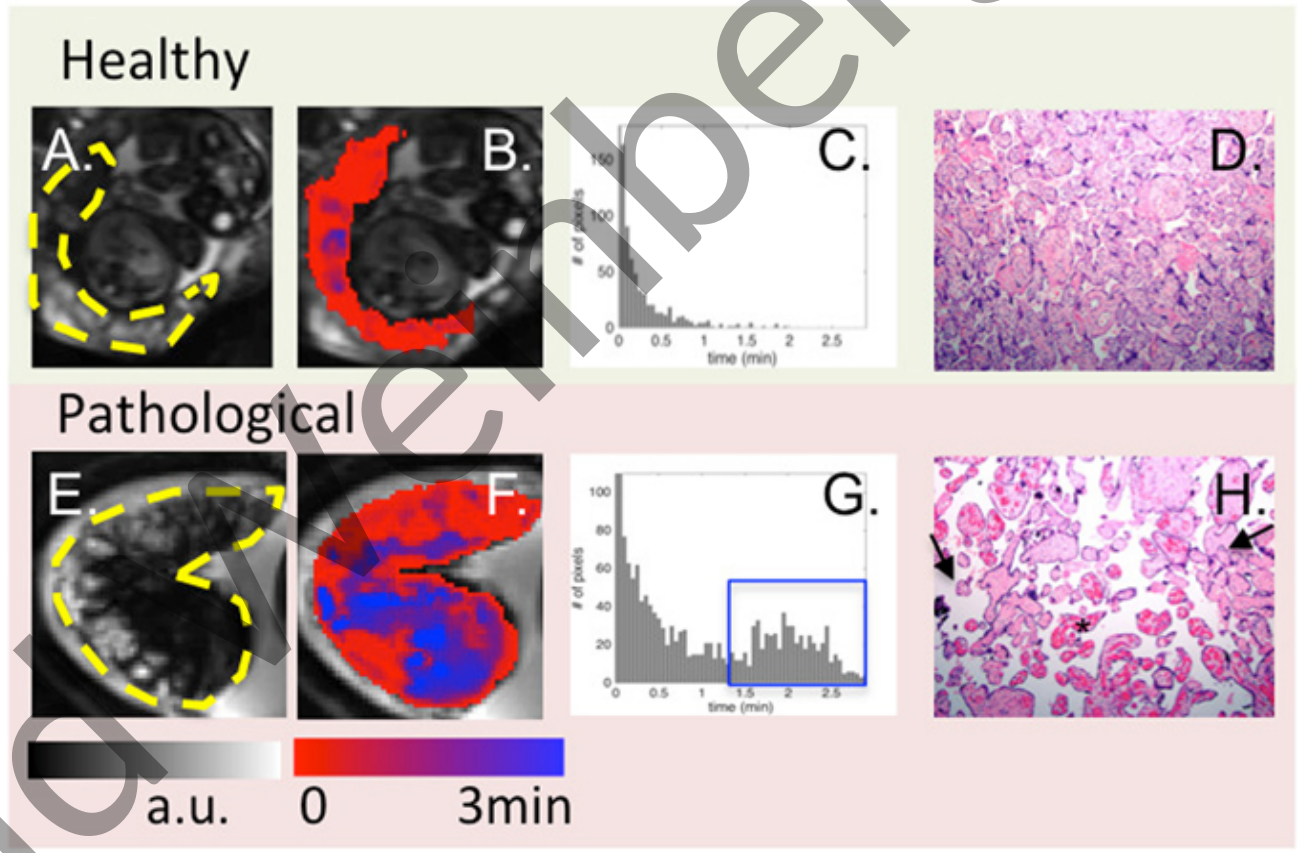
Applying Cutting-edge MRI Technologies to Placental Assessment

Blood Oxygen Level Dependent (BOLD) MRI

- Advanced motion correction
- Connecting placental function to outcomes



From left to right: BOLD images, TTP maps, histogram of TTP distribution and histology (10X). One control (top) is compared to one case with abnormal placental pathology (bottom). Yellow dashes in A and E outline the placenta. For healthy subjects, TTP values were short and placental histology was normal. For pathological cases, TTP values were longer and less uniform (blue regions in (**F**) and blue box in (**G**)). Arrows in H point to avascular villi and the star identifies chorangiosis.

In Vivo Quantification of Placental Insufficiency by BOLD MRI: A Human Study. Science Reports 2017 7(1):3713

Ellen Grant, Harvard Medical School - HPP Grantee

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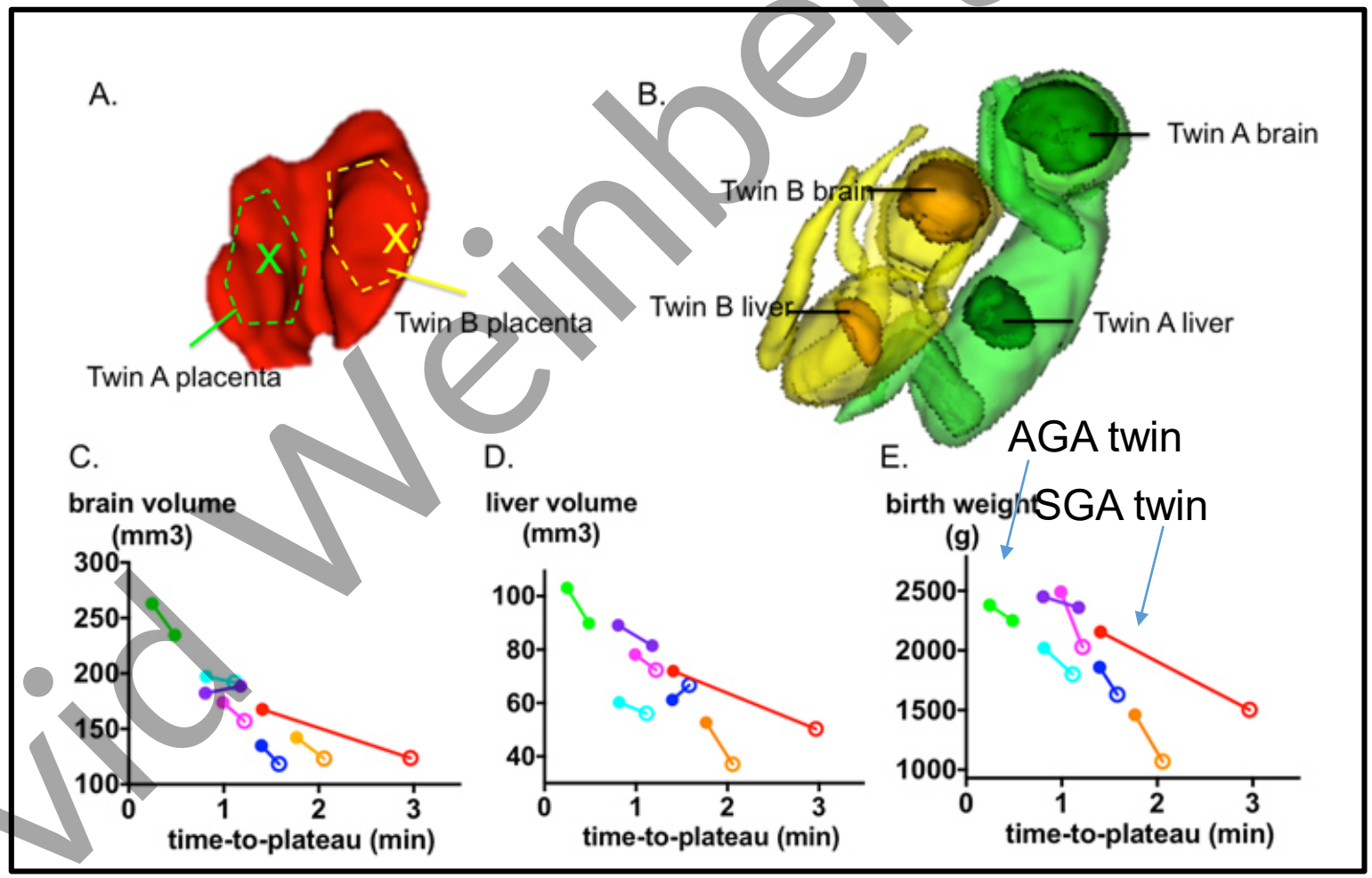
Applying Cutting-edge MRI Technologies to Placental Assessment

Discordant monozygotic monochorionic, diamniotic twins

- **Connecting placental function to outcomes**



In Vivo Quantification of Placental Insufficiency by BOLD MRI: A Human Study. Science Reports 2017 7(1):3713

Ellen Grant, Harvard Medical School - HPP Grantee

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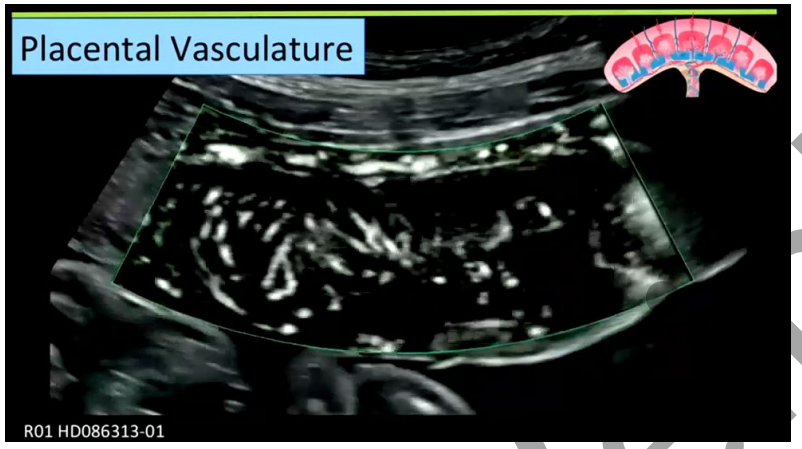
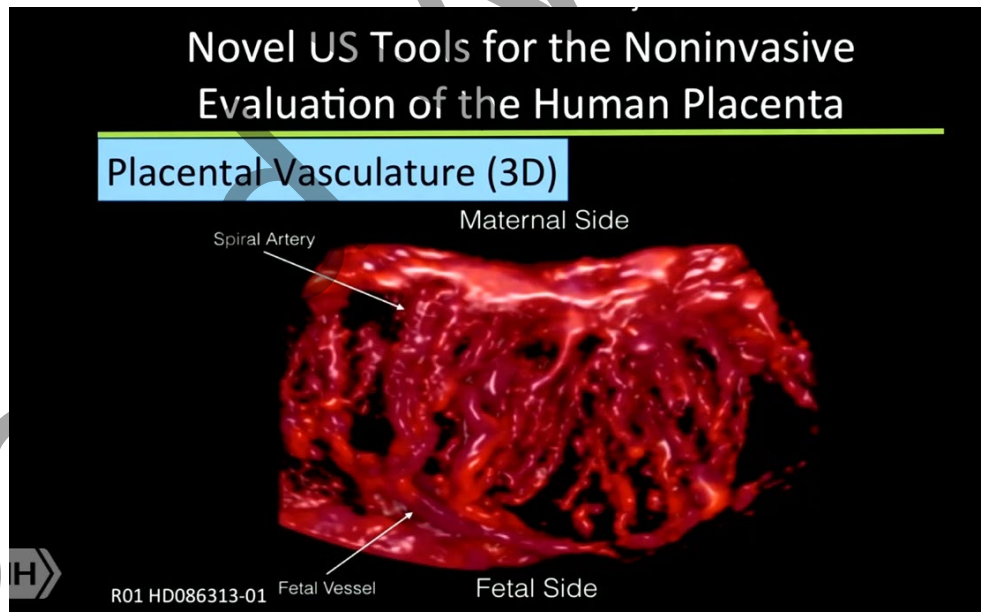
Applying Cutting-edge Ultrasound Technologies to Placental Assessment

Superb Microvascular Imaging





- 15-16 weeks gestation – can visualize both fetal and maternal circulation
- Can count spiral arteries, fetal arterioles, and do quantitation with doppler techniques
- Generate a vascular index – the degree of vascularity for a given region of the placenta

Allows assessment of the overall health of the

Do Not Members

Applying Cutting-edge Ultrasound Technologies to Placental Assessment: Superb Microvascular Imaging

Applied to Normal versus preterm births

Goals: Normograms

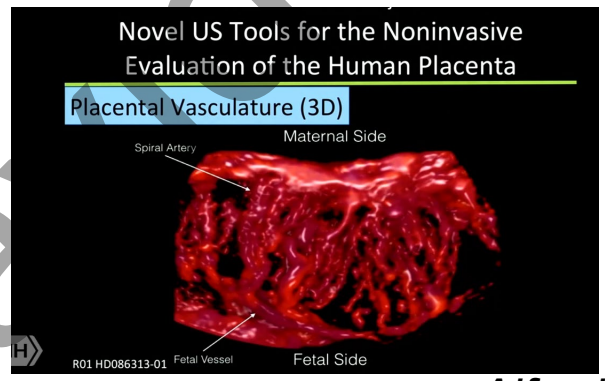
Selection of USEFUL clinical measurements

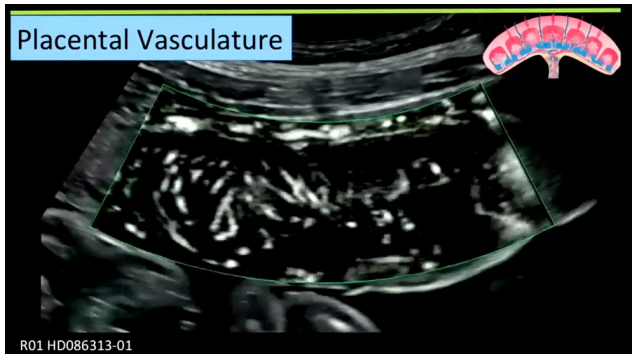
Development of a pregnancy index

Total Enrollment: **620**
Pregnancies for Normograms: **130**
Cases: **130**
Controls: **490**

8 ultrasound sessions from 12 weeks to 37 weeks

- Deep phenotyping:
  - Biometry
  - Vasculature – spiral arteries, Fetal arterioles
  - Tissue Density
  - Genetics
  - Calcification
  - Fetal Echo
  - Cell free RNA analysis
  - Placental pathology
  - Urine sample for phenol exposure study (with NIEHS)
  - Pregnancy outcome and maternal history data





Alfred Abuhamad, EVMS – George Saade UTMB HPP Grar

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Exosome Isolation of Placental Health

Cargo of miRNAs, lipids, proteins may reflect placental health

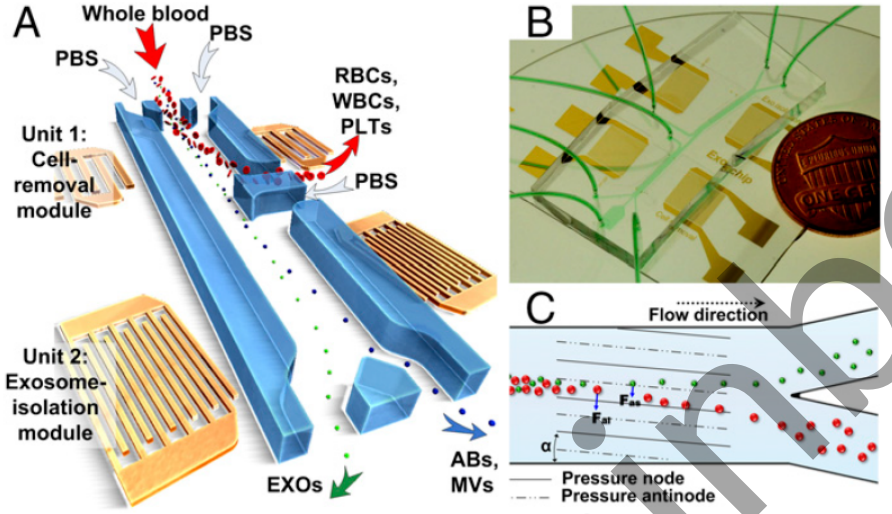

Fig. 1. Schematic illustration and mechanisms underlying integrated acoustofluidic device for isolating exosomes. (*A*) RBCs, WBCs, and PLTs are filtered by the cell-removal module, and then subgroups of EVs (ABs: apoptotic bodies; EXOs: exosomes; MVs: microvesicles) are separated by the exosome-isolation module. (*B*) An optical image of the integrated acoustofluidic device. Two modules are integrated on a single chip. (*C*) Size-based separation occurs in each module due to the lateral deflection induced by a taSSAW) field. The periodic distribution of pressure nodes and antinodes generates an acoustic radiation force to push large particles toward node planes.

Isolation of exosomes from whole blood by integrating acoustics and microfluidics PNAS 114(40):10684 2017

- **Gentle, high yield approach**
- **Works for vesicles from any source circulating in blood**

Yoel Sadovsky and Tony Huang, HPP Grantees

Acousto-fluidics – Biotechnology *applied to the placenta and pregnancy*

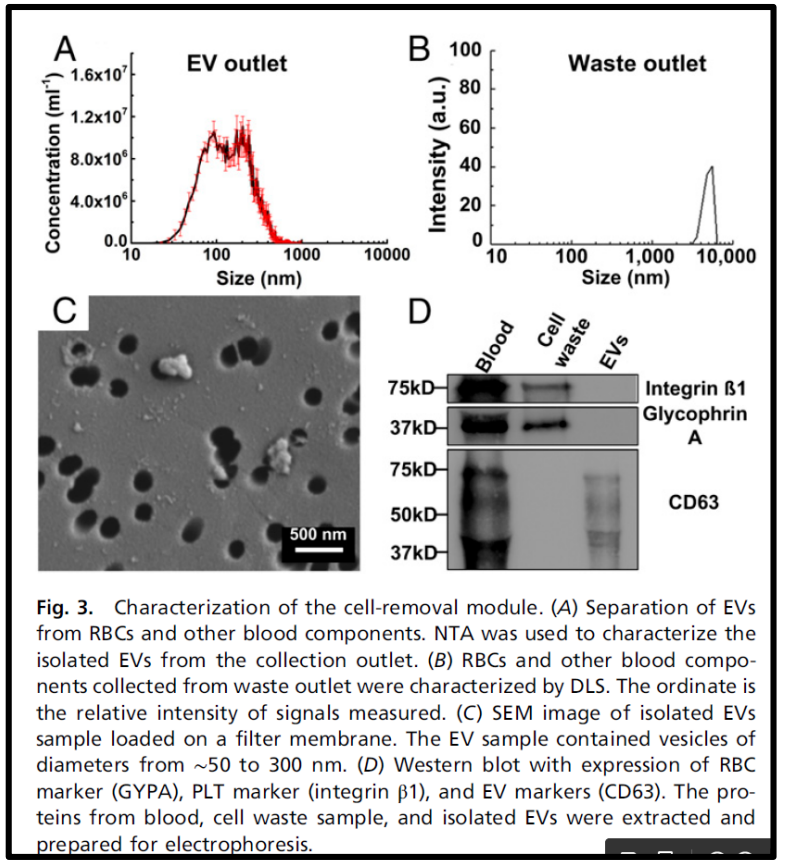

Fig. 3. Characterization of the cell-removal module. (*A*) Separation of EVs from RBCs and other blood components. NTA was used to characterize the isolated EVs from the collection outlet. (*B*) RBCs and other blood components collected from waste outlet were characterized by DLS. The ordinate is the relative intensity of signals measured. (*C*) SEM image of isolated EVs sample loaded on a filter membrane. The EV sample contained vesicles of diameters from ~50 to 300 nm. (*D*) Western blot with expression of RBC marker (GYPA), PLT marker (integrin β1), and EV markers (CD63). The proteins from blood, cell waste sample, and isolated EVs were extracted and prepared for electrophoresis.

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Tried and True Approaches: MRI

Quantitative longitudinal T2* mapping for assessing placental function and association with adverse pregnancy outcomes across gestation. Schabel MC, Roberts VHJ, Gibbins KJ, Rincon M, Gaffney JE, Streblow AD, Wright AM, **Lo JO**, Park B, Kroenke CD, Szczotka K, Blue NR, Page JM, Harvey K, Varner MW, Silver RM, Frias AE.PLoS One. 2022 Jul 19;17(7):e0270360

Chronic prenatal delta-9-tetrahydrocannabinol exposure adversely impacts placental function and development in a rhesus macaque model. Roberts VHJ, Schabel MC, Boniface ER, D'Mello RJ, Morgan TK, Terrobias JJD, Graham JA, Borgelt LM, Grant KA, Sullivan EL, **Lo JO.**Sci Rep. 2022 Nov 24;12(1):2026

T2*-weighted placental MRI: basic research tool or emerging clinical test for placental dysfunction? Sørensen A, Hutter J, Seed M, **Grant PE**, Gowland P.Ultrasound Obstet Gynecol. 2020 Mar;55(3):293-302

Human Placenta Blood Flow During Early Gestation With Pseudocontinuous Arterial Spin Labeling MRI. Liu D, Shao X, Danyalov A, Chanlaw T, Masamed R, Wang DJJ, Janzen C, Devaskar SU, Sung K.J Magn Reson Imaging. 2020 Apr;51(4):1247-1257

Evaluation of Spatial Attentive Deep Learning for Automatic Placental Segmentation on Longitudinal MRI. Liu Y, Zabihollahy F, Yan R, Lee B, Janzen C, Devaskar SU, Sung K.J Magn Reson Imaging. 2023 May;57(5):1533-1540

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Tried and True Approaches: Ultrasound

Fully Automated 3-D Ultrasound Segmentation of the Placenta, Amniotic Fluid, and Fetus for Early Pregnancy Assessment. Looney P, Yin Y, **Collins SL**, Nicolaides KH, Plasencia W, Molloholli M, Natsis S, Stevenson GN.IEEE Trans Ultrason Ferroelectr Freq Control. 2021 Jun;68(6):2038-2047

Volume and vascularity: Using ultrasound to unlock the secrets of the first trimester placenta.Mathewlynn S, **Collins SL.**Placenta. 2019 Sep 1;84:32-36

Longitudinal assessment of spiral artery and intravillous arteriole blood flow and adverse pregnancy outcome.**Odibo AO**, Kayisli U, Lu Y, Kayisli O, Schatz F, Odibo L, Chen H, Bronsteen R, Lockwood CJ.Ultrasound Obstet Gynecol. 2022 Mar;59(3):350-357

Placenta Accreta Spectrum: Prenatal Diagnosis and Management.Horgan R, Abuhamad A.Obstet Gynecol Clin North Am. 2022 Sep;49(3):423-438

Minimally interactive placenta segmentation from three-dimensional ultrasound images.Oguz I, Yushkevich N, Pouch A, Oguz BU, Wang J, Parameshwaran S, Gee J, Yushkevich PA, **Schwartz N.**J Med Imaging (Bellingham). 2020 Jan;7(1):014004

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Tried and True Approaches: Circulating Factors

Biosensors for Detection of Human Placental Pathologies: A Review of Emerging Technologies and Current Trends. Liu J, Mosavati B, Oleinikov AV, Du E. Transl Res. 2019 Nov;213:23-49

Chronic prenatal delta-9-tetrahydrocannabinol exposure adversely impacts placental function and development in a rhesus macaque model. Roberts VHJ, Schabel MC, Boniface ER, D'Mello RJ, Morgan TK, Terrobias JJD, Graham JA, Borgelt LM, Grant KA, Sullivan EL, **Lo JO.** Sci Rep. 2022 Nov 24;12(1):2026

MicroRNAs in placental health and disease. Mouillet JF, Ouyang Y, Coyne CB, Sadovsky Y. Am J Obstet Gynecol. 2015 Oct;213(4 Suppl):S163-72

Circulating Placental Extracellular Vesicles and Their Potential Roles During Pregnancy. Nakahara A, Nair S, Ormazabal V, Elfeky O, Garvey CE, Longo S, Salomon C. Ochsner J. 2020 Winter;20(4):439-445.

Placental protein levels in maternal serum are associated with adverse pregnancy outcomes in nulliparous patients. Parry S, Carper BA, Grobman WA, Wapner RJ, Chung JH, Haas DM, Mercer B, Silver RM, Simhan HN, Saade GR, Reddy UM, Parker CB; Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be Group. Am J Obstet Gynecol. 2022 Sep;227(3):497.e1-497.e13

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New Models: Organ-on-a-Chip

Organ-on-a-chip for perinatal biology experiments. Menon R, Richardson L. Placenta Reprod Med. 2022 Jul 6;1:9

Microphysiological modeling of the reproductive tract: a fertile endeavor. Eddie SL, Kim JJ, **Woodruff TK**, Burdette JE. Exp Biol Med (Maywood). 2014 Sep;239(9):1192-202

Development of a novel dual reproductive organ on a chip: recapitulating bidirectional endocrine crosstalk between the uterine endometrium and the ovary. Park SR, Kim SR, Lee JW, Park CH, Yu WJ, Lee SJ, Chon SJ, Lee DH, Hong IS. Biofabrication. 2020 Oct 16;13(1)

Dynamic placenta-on-a-chip model for fetal risk assessment of nanoparticles intended to treat pregnancy-associated diseases. Shojaei S, Ali MS, Suresh M, Upreti T, Mogourian V, Helewa M, Labouta HI. Biochim Biophys Acta Mol Basis Dis. 2021

Drug transport across the human placenta: review of placenta-on-a-chip and previous approaches. Pemathilaka RL, Reynolds DE, Hashemi NN. Interface Focus. 2019 Oct 6;9(5)

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Organoids as Tools to Study Developmental Origins

Modeling Development and Disease with **Organoids**.Clevers H.Cell. 2016 Jun 16;165(7):1586-1597

“Recent advances in 3D culture technology allow embryonic and adult mammalian stem cells to exhibit their remarkable self-organizing properties, and the resulting organoids reflect key structural and functional properties of organs such as kidney, lung, gut, brain and retina. Organoid technology can therefore be used to model human organ development and various human pathologies 'in a dish." Additionally, patient-derived organoids hold promise to predict drug response in a personalized fashion. Organoids open up new avenues for regenerative medicine and, in combination with editing technology, for gene therapy. The many potential applications of this technology are only beginning to be explored.”

Hans Clevers, Hubrecht Institute/Royal Netherlands Academy of Arts and Sciences, Princess Maxima Centre and University Medical Centre Utrecht, 3584CT Utrecht, The Netherlands

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New Models: Organoids

Scaffold-Free Endometrial Organoids Respond to Excess Androgens Associated With Polycystic Ovarian Syndrome. Wiwatpanit T, Murphy AR, Lu Z, Urbanek M, Burdette JE, **Woodruff TK**, Kim JJ. J Clin Endocrinol Metab. 2020 Mar 1;105(3):769-80

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