Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** Magee-Womens Research Institute and Foundation

2. **Reporting Period (start and end date of grant award period):** 1/1/13-12/31/13

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Cheryl A. Richards, MBA

4. **Grant Contact Person's Telephone Number:** 412-641-8932

5. **Grant SAP Number:** 4100062212

6. **Project Number and Title of Research Project:** Project 1 - Maternal lipids and placental function

7. **Start and End Date of Research Project:** 1/1/13-12/31/13

8. **Name of Principal Investigator for the Research Project:** Janet Catov, PhD

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 139,055.01

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Catov, Janet	Principal Investigator	30%	$26,985
Peng, Ye	Data Administrator	50%	$23,820
Derzic, Karen	Research Coordinator	100%	$39,242

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project
Tony Parks	Collaborator	1%
Claudia Holzman	Collaborator	1%
Patricia Senegore	Collaborator	1%
Karen Florio	Fellow	5%

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No_____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
None	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes__X_____ No_____

If yes, please describe your plans:

In the coming year, we plan to submit an NIH application to leverage the linked perinatal registry and placenta data, once linkage to the available biospecimens is achieved (underway for 2014).

12. Future of Research Project. What are the future plans for this research project?

The research team has plans to publish results from specific aims 1 and 2 in order to share the newly developed protocol with other researchers. In addition, we will continue to share our findings from specific aim 3 with researchers inside and outside of our institution.
Drs. Parks and Catov have decided to continue their collaboration. A paper is in development (due June 2014) to describe the linkage of placental pathology data to hospital registry data to support innovative investigations into the etiology of pregnancy complications and abnormalities of fetal development. In addition, specific next projects include the identification of placental characteristics related to maternal cancers, gastroschesis, gestational diabetes, and gestational weight gain.

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes____X____ No___ _____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				1
Unknown				
Total				**1**

	Undergraduate	Masters	Pre-doc	Post-doc
White				1
Black				
Asian				
Other				
Unknown				
Total				**1**

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No____X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes__X_____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

Developing the infrastructure to link MOMI records to placental pathology records has been established and will afford a more robust dataset to researches. Indeed, this newly linked data has now been requested by two investigators studying fetal growth and gestational diabetes. By including information on placenta pathology, we will be able to provide a more complete picture of pregnancy and delivery to researchers.

In addition, our project extends the capacity of the placental pathology department to standardize the identification of syncytial knots in order to recognize vascular underperfusion. Efforts are underway to validate this approach against the standard clinical approach.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes___X_____ No_____

If yes, please describe the collaborations:

The established collaboration between Dr. Janet Catov and Dr. Tony Parks has provided Dr. Parks with the knowledge required to create an enhanced system to record placental pathology data. Currently the system is an open-field document where the data must be hand or computer abstracted to achieve the results in specific aim 2 of this study. Dr. Parks has since approached his department to develop a synoptic system to capture relevant information in checkboxes and yes/no questions. The synoptic is currently being built and should be used beginning in 2014. Once this is in place, the ability to link MOMI records to placental pathology will be easier and the results will be consistent across pathologists and over time.

In addition, our study supported collaboration with Michigan State University that allowed us to undertake an inter-rater reliability study to test the reproducibility of a quantitative approach to assess excess syncytial knots relevant to placental underperfusion. A manuscript summarizing these results is underway.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No____X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No____X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Specific Aim 1: To validate a quantitative approach to evaluation of syncytial knots in placentas delivered at term (≥ 37 weeks) and preterm (<37 weeks), stratified by the presence and absence of hypertension.

The Pregnancy Outcomes and Community Health (POUCH) study prospectively recruited 3,019 pregnant women in mid-pregnancy from 52 clinics in five Michigan communities (1998-2004). A subcohort (n=1219) was selected for placental pathology review, which was conducted by a single pathologist, Dr. Pat Senegore, following a rigorous research protocol. We used these specimens for this project.

The research teams in Pittsburgh and Michigan met regularly to develop the protocol to quantify syncytial knots in placentas using the published approach. The final study groups are outlined below. The team in Michigan randomly selected 20 placental specimens from each group for evaluation by both study pathologists.

Term (37-40 weeks), no prominent syncytial knots in the disc section
Term, diffuse prominent syncytial knots with lesion in the disc section
Term, diffuse prominent syncytial knots without lesion
Term, diffuse prominent syncytial knots with and without lesions

Preterm (34-36; 26-33; 20-25), no prominent syncytial knots in the disc section
Preterm, diffuse prominent syncytial knots with lesion in the disc section
Preterm, diffuse prominent syncytial knots without lesion
Preterm, diffuse prominent syncytial knots with and without lesions

Drs. Senagore and Parks finalized the protocol for Specific Aim 1. Both pathologists reviewed 20 randomly selected slides and systematically recorded the number of chorionic villi that contained one or more syncytial knots (SK) out of 100. Results were compared and discrepancies resolved in order to finalize the study protocol. Next, the team in Michigan randomly selected 20 placental specimens for each study group (total specimens, n=153). One pathologist, Dr. Senagore, then drew a grid over the central portion of one section of each specimen. This grid was comprised of ten 2 x 2 mm squares. Each pathologist counted the number of SKs in each grid square. To do so, the pathologist first centered his or her microscope field of view at 10x over the grid (Figure 1). He or she then switched to 40x for the actual counts (Figure 2). At that power, around 10 terminal villi will be visible in the field. The number of terminal villi containing at least one SK were then counted. Dysmature or immature intermediate villi were counted if the terminal villi were not present. An average of 10 terminal villi were evaluated for each grid square, yielding 100 total terminal villi examined per specimen. The pathologists completed the counts using the Loukeris count, where SKs are

counted when they contact another villus, but only in a minimal/partial fashion and the contour/geometry of the nuclear aggregate is such that it does not suggest a fusion of syncytiotrophoblast nuclei from an adjacent villus. The suggestion or presence of a thin clear space or nucleus-free cytoplasm between the SK and the contacting villus aided in making this decision. In addition, a "bridging" count was recorded that comprised those additional nuclear aggregates that fulfilled the most of the previous criteria but were not allowed because contact with another villus suggested fusion or syncytial "bridge" formation. The total SK count, Loukeris + bridging, was equal to or less than 10 per 2x2 mm square. Samples of SKs are identified in Figure 2.

The correlation between the two pathologist results of each SK count (Loukeris, bridging, and total) were 0.76, 0.62, and 0.72 (all $p<0.01$) indicating strong to moderate correlation. These results confirm that this quantitative approach to assessing SKs has good reproducibility. The bridging counts contained the most discrepancies, and our team is examining these in more detail. There is evidence, for example, that bridging SKs may be independently related to underperfusion and preterm birth.

Specific Aim 2: To identify placentas delivered at term and preterm with excess syncytial knots, and correlate these with clinical evidence of maternal hypertension, excess lipids, and impaired fetal growth.

The average total SK count (average of two pathologists) was significantly higher in cases of hypertension (preeclampsia, gestational hypertension, and chronic hypertension, n=28) compared to normotensive cases (57.2 [SD 12.8] vs. 41.6 [SD 14.7], $p <0.01$). In addition, placentas from women who delivered small-for-gestational-age infants, known to be associated with placental underperfusion, had higher SK counts compared to placentas from women who delivered infants who were average for gestational age (50.1 vs. 43.7, $p=0.08$). On average, Caucasian women had modestly higher SK counts than African American women (46.3 vs. 41.1, $p=0.05$). SK counts tended to increase modestly as maternal age increased ($r=0.20$, $p=0.01$). SK counts did not differ by pre-pregnancy BMI or infant sex.

We then compared the quantitative SK measurement to the research protocol used in the POUCH study, which identified a dichotomous variable of prominent SK (presence/absence; Table 1). As expected, mean count of SKs was highest in the groups with excess SK noted following the research protocol (range 47.9 to 53.2) and the lowest counts were in term and preterm samples with no excess SK noted (29.1 and 22.8). Consistent with these results, the proportion of placental specimens evaluated that were above the normal ranges proposed by Loukeris, et al. was very high in cases with noted excess SK and lower in those with no excess SK noted. Of note, using these reference ranges, 63.2% of preterm placental samples without infarcts and not identified, using the research protocol, as having excess SKs were identified as having excess SKs using the quantitative approach. These may comprise a group of preterm delivery cases related to underperfusion that the new approach identified. In addition, when relating the quantitative SK count to the presence of hypertension, another possible benefit of a continuous count (as compared to a dichotomous presence/absence) was noted. Independent of gestational age and the presence of infarcts, each 5-unit increment in the SK count was associated with an increased risk of hypertension (odds ration 1.43, 95% CI 1.16, 1.76).

Our results indicate that this quantitative approach to assessing SKs is reliable and reproducible and provides a validated approach to identifying a marker of vascular underperfusion that is strongly associated with hypertension. This is a critical step in identifying a subgroup of spontaneous preterm deliveries that may be related to underperfusion. This is important, as identifying this subgroup has been hindered by the lack of reliable, reproducible evidence of underperfusion in cases without overt infarcts. Efforts are now underway to relate SK counts to maternal lipids and inflammatory markers measured in serum collected during pregnancy.

Specific Aim 3: To link deliveries at Magee-Womens Hospital with placental pathology data in order to incorporate placental data into population studies of preterm birth.

Since 1995, the Magee Obstetrical Medical and Infant Database (MOMI) database has served as a registry of births at Magee-Womens Hospital. The database contains over 300 variables describing prenatal care, delivery, and infant characteristics for 135,000 births. Records are identified via a unique medical record number and can be de-identified for research purposes.

We estimated that placental specimens are routinely evaluated for approximately 50% of deliveries at Magee-Womens Hospital, although this has never been quantified because the systems that track delivery data are not linked to the pathology system. Magee-Womens Hospital protocol recommends placental specimens be routinely examined by pathology in cases of pre-term delivery (<37 weeks), pre-eclampsia, gestational diabetes, fetal growth restriction, and a variety of other conditions complicating pregnancy. Pathology reports following these examinations include a descriptive narrative of the results, which report weight, length, and thickness of the placenta, as well as diagnoses and presence or absence of inflammatory and vascular lesions. The reports are labeled with the patients' medical record number and are stored as text file reports. To date, research review of these records has required manual record abstraction.

In order to create a more complete report of pathology related to pregnancy and delivery complications, the goal of this project is to electronically link placental pathology data to MOMI delivery data for all births that have a pathology report.

A research team was assembled to outline the protocol for the study. All deliveries and pathology records from 2008 through 2012 were included, as all pathology evaluations during this time period were conducted by two pathologists. This allows for inter-rater comparisons, and ensures consistency in reporting, and therefore, these records are best suited for automated data extraction. The University of Pittsburgh IRB approved the project, and the team has worked with the Center for Assistance in Research using eRecord (CARe) to identify and pull the available pathology reports.

The CARe team delivered 30,000 placenta pathology reports in text file format. The data administrator then began the linkage to MOMI records and the data extraction process. The text reports were matched by medical record number to the existing MOMI cohort. While the information contained in the pathology report is consistently documented, there are not discrete fields for the data. Therefore, the data were extracted from the reports into a data set for

analysis. This programming-intensive step first combined the individual text placental pathology reports into one text file and these were then translated into Extensible Markup Language (XML) script using Java. The XML file acts as a staging area where the data were then transformed and cleaned using an XML schema. A structured query language (SQL) was then used to transform the text information into variables which were extracted and placed into separate tables for each section of the text reports (header, report details, description, and diagnosis). Lastly, the COGNOS framework, Web-based software for creating and managing custom reports, was used to link the variables from the placental pathology reports to the variables in the MOMI database. The process is shown in Figure 3. The complete data set was then used for analysis.
We have quantified the MOMI records with and without placenta pathology reports. There were 47,329 deliveries during 2008-2012, and overall, 45.39% of these have accompanying placental pathology reports (n=21,585). Table 2 presents these deliveries according to gestational week. The proportion of term births (37-42 weeks) with placental pathology reports ranged from 41.0%-59.6%. As expected, among preterm deliveries (19-36 weeks), the proportion with placental pathology reports ranged from 84.1% to 100%. Of note, pathology reports were available for ≥ 95% of births delivered at or before 35 weeks' gestation. For the first time, we have quantified the availability of placental pathology reports among Magee deliveries, a critical first step to incorporating these data into our research registry.

Table 3 presents maternal characteristics according to deliveries with and without placental pathology reports. These reports were available for 5,108 preterm deliveries (93%) and for 14,019 term deliveries (37.1%). Deliveries to smokers compared to non-smokers were more likely to have placental pathology reports (57 vs. 43%), and deliveries to African American women were more likely to have pathology reports compared to deliveries to Caucasian women (50.8 vs. 44.0%). In addition, over 90% of deliveries to women with hypertension (chronic hypertension and mild or severe preeclampsia) were likely to have pathology reports. Deliveries to women with gestational hypertension compared to normotensive women were also more likely to have pathology reports (57.2 vs. 40.8%).

As expected, deliveries with placental pathology reports were delivered earlier compared to those without these reports (mean gestational age 37.65 [SD 3.62] vs. 39.13 [2.61] weeks, $p<0.001$) and infants were smaller (3060 [852] vs. 3423 [448] g, $p<0.001$). Women with deliveries having pathology reports were, on average, slightly younger compared to those without reports (Table 4 and Figure 4). They also had a higher pre-pregnancy body mass index (BMI 26.3 [6.56] vs. 24.87 [5.51] kg/m², $p<0.001$) compared to their counterparts with deliveries without pathology reports.

The MOMI/Placenta database is organized by patient identification number and contains basic information such as pre-natal weight, maternal smoking status, gestational age at delivery, and birth weight. In addition, there are descriptive details of the placenta and cord, as well as extracted information regarding types of lesions diagnosed. These have been grouped into inflammatory lesions (n=10,731) and non-inflammatory lesions (n=7,127). Table 5 summarizes the lesions identified and included; validation of the specific lesion diagnosis is currently underway.

Using this MOMI/Placenta database, we identified a new subset of deliveries from Magee-Womens Hospital, representing term and preterm deliveries, with and without infarcts and with and without advanced villious maturation (n=135). These cases were chosen to branch both specific aims 1 and 3 of this project. A single placental pathologist, Dr. Tony Parks, replicated the quantitative SK counts to compare to the Loukeris normal ranges for gestational age. This will provide the test case for comparing a general clinical protocol (not a research protocol) that assesses excess SKs to the quantitative approach. Results for this analysis are summarized in Table 6. Our results indicate that the quantitative approach reasonably reflects the clinical approach for preterm births, but results for term births are more discrepant. Our team is identifying another set of 135 specimens to be evaluated, and plans to utilize these records to manually validate the placental data extracted from placental pathology reports.

These data have already been used by a Maternal and Fetal Medicine fellow to fulfill her research requirement. We linked the MOMI/Placenta database to the Genetics Information System data in order to compare pregnancy-associated plasma protein A (PAPP-A) results from the first trimester to characteristics of the placenta (dimensions and lesions). Two abstracts, "First trimester pregnancy associated plasma protein A (PAPP-A) and placental size in women with adverse pregnancy outcomes" and "Low first trimester PAPP-A does not predict adverse pregnancy outcome in high risk women," were accepted for the 2014 Society of Gynecologic Investigation (Florence, Italy) for poster presentations.

In addition, analysis is being completed which links the Prenatal Exposures and Preeclampsia Prevention (PEPP3) project at Magee-Womens Hospital to the placental pathology data to relate placental characteristics to gestational weight gain and the inflammatory signature measured in women 6 months after delivery (balance of pro-inflammatory [Interlekin-2, Interleukin-6, Interferon-gamma] and anti-inflammatory cytokines [Interleukin-1 receptor antagonist, Interleukin 10]).

Our project also now includes a component to design, test, and implement a synoptic data collection mechanism in the pathology system that will prospectively capture these data as discrete variables to facilitate linkage to delivery data in the future.

Figure 1. 10 2x2mm squares in grid

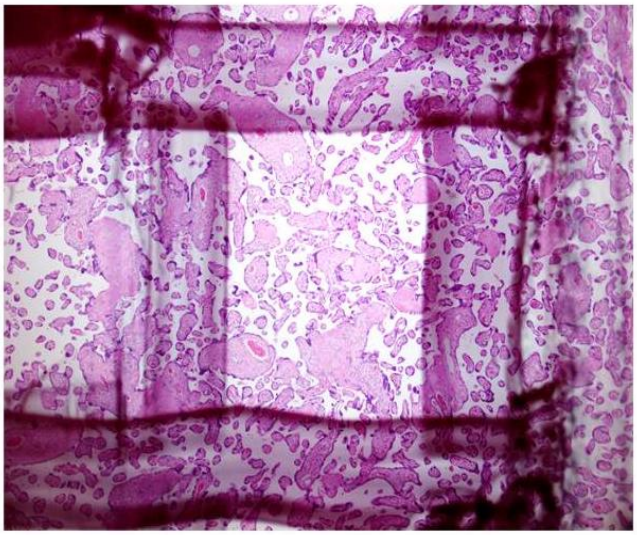
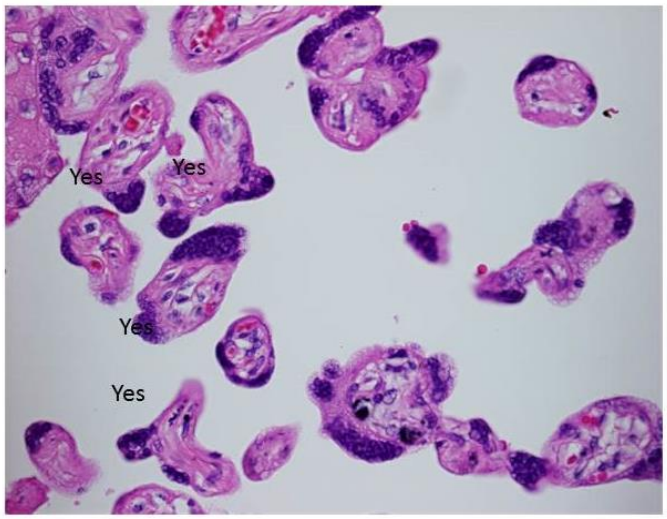


Figure 2. 40x center field



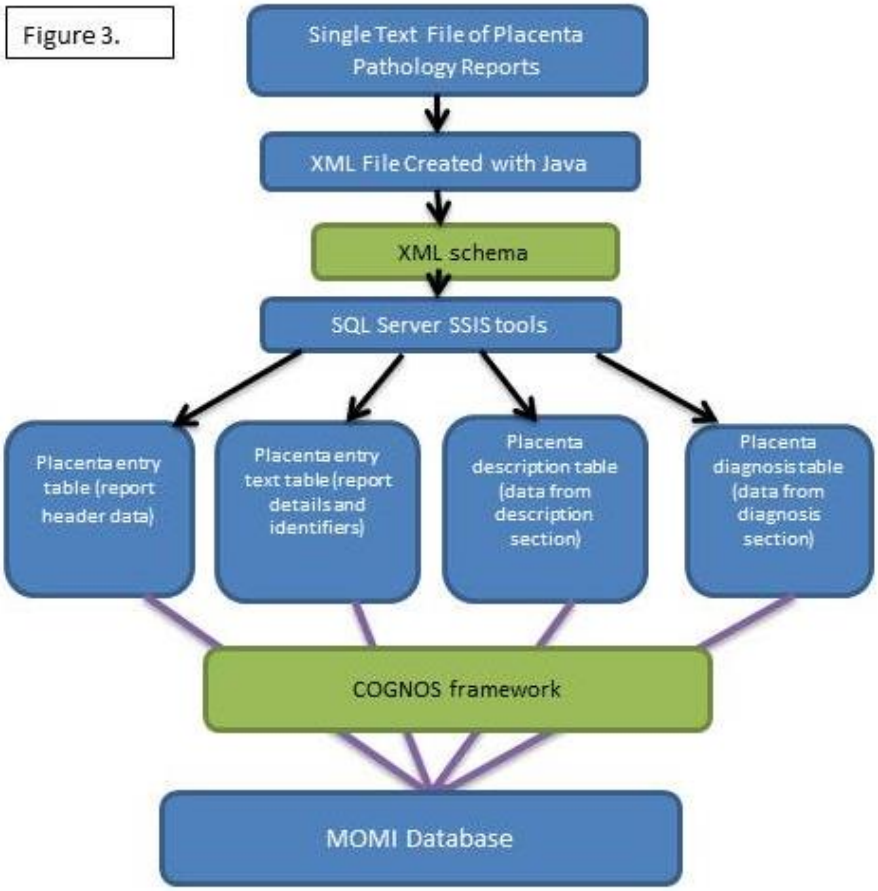


Table 1. Quantitative vs. research diagnosis of excess syncytial knots in term and preterm placenta

			Research Diagnosis		Quantitative SK count	
Group	Term	n	Infarct	Prominent SK	Mean (SD)	n (%) above normal range
1	Term	20	-	-	29.1 (2.4)	8 (40.)
2	Term	20	+	+	53.2 (2.5)	20 (100)
3	Term	19	-	+	49.4 (2.5)	17 (89.5)
4	Term	20	+/-	+	51.1 (2.5)	17 (85.0)
5	Preterm	19	-	-	22.8 (2.5)	12 (63.2)
6	Preterm	16	+	+	49.3 (2.8)	13 (81.3)
7	Preterm	19	-	+	47.9 (2.5)	17 (89.5)
8	Preterm	18	+/-	+	54.7 (2.6)	18 (100)

Table 2. MOMI records with and without placental pathology, according to gestational age at delivery

Weeks' gestation at delivery	MOMI records with placenta pathology reports, n (%)	MOMI records without placenta pathology reports, n (%)	Total
19	23 (100)	0 (0)	23
20	15 (100)	0 (0)	15
21	26 (96.30)	1 (3.70)	27
22	30 (96.77)	1 (3.23)	31
23	41 (100)	0 (0)	41
24	75 (100)	0 (0)	75
25	85 (100)	0 (0)	85
26	92 (100)	0 (0)	92
27	80 (97.56)	2 (2.44)	82
28	102 (98.08)	2 (1.92)	104
29	153 (98.71)	2 (1.29)	155
30	158 (98.14)	3 (1.86)	161
31	268 (98.89)	3 (1.10)	271
32	352 (98.32)	6 (1.68)	358
33	439 (98.21)	8 (1.79)	447
34	705 (98.46)	11 (1.54)	716
35	888 (94.87)	48 (5.13)	936
36	1,554 (84.05)	295 (15.95)	1,849
37	2,382 (57.73)	1,744 (42.27)	4,126
38	2,842 (41.02)	4,087 (58.98)	6,929
39	5,270 (33.15)	10,630 (66.86)	15,900
40	3,828 (37.42)	6,401 (62.58)	10,229
41	1,901 (43.35)	2,484 (56.65)	4,385
42	174 (59.59)	118 (40.41)	292
Total	**21,483 (45.39)**	**25,846 (54.61)**	**47,329**

Table 3. Characteristics of deliveries with and without placenta pathology reports (2008-2012)			
	With Placenta Pathology Report, n (%)	**Without Placenta Pathology Report, n (%)**	**Total MOMI Records, n (%)**
Pre-Term (<37 weeks)	5108 (93)	386 (7)	5494
Term (≥37 weeks)	14019 (37.1)	23720 (62.9)	37739
Smoker	3295 (57)	2489 (43)	5784
Non-smoker	15085 (43)	19932 (57)	35017
Caucasian	15131 (44)	19263 (56)	34394
African American	4655 (50.8)	4502 (49.2)	9157
Other	1189 (44)	1516 (56)	2705
No Hypertension	16921 (40.8)	24595 (59.2)	41516
Gestational hypertension	1446 (57.2)	1081 (42.8)	2527
Preeclampsia mild	1733 (91.3)	165 (8.7)	1898
Preeclampsia severe	960 (98)	20 (2)	980
Eclampsia	35 (97.2)	1 (2.8)	36
Chronic hypertension with preeclampsia	450 (97)	14 (3)	464

Table 4. Infant and maternal characteristics, according to deliveries with and without placental pathology reports								
	With Placenta Pathology Report				**Without Placenta Pathology Report**			
	N	**Mean**	**Std. Deviation**		**N**	**Mean**	**Std. Deviation**	***p*-value**
Gestational Age at Delivery	21522	37.65	3.62		25859	39.13	2.61	<0.001
Infant Birth Weight	21542	3060.42	852.61		25874	3423.91	448.37	<0.001
Maternal Age	21536	28.46	6.06		25870	28.84	5.76	<0.001
Maternal Height	21370	57.84	19.69		25738	59.79	17.28	<0.001
Pre-Pregnancy BMI	11226	26.30	6.56		15647	24.87	5.51	<0.001

Figure 4. Distribution of Mother's Age

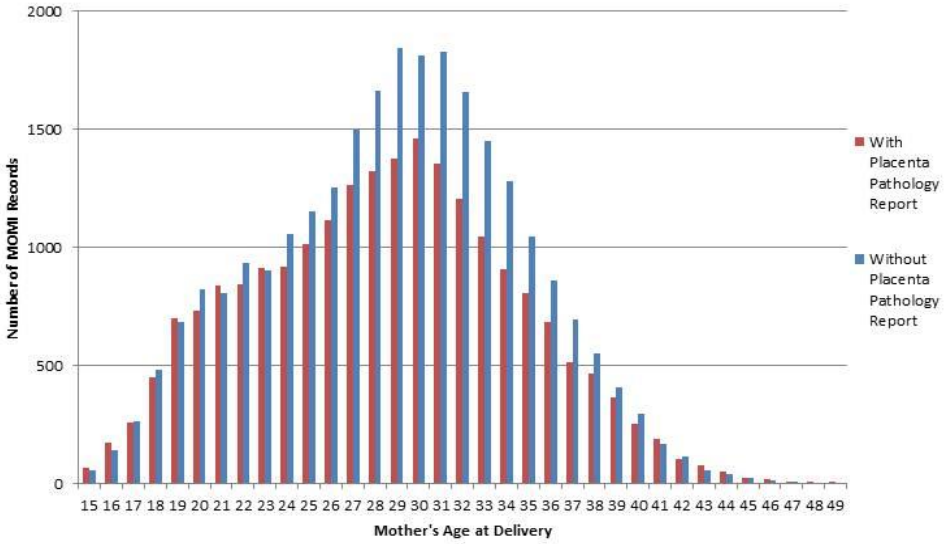


Table 5. MOMI/Placenta database, maternal characteristics and types of lesions 2008-2012	
	N=21,584
<37 Weeks Gestational Age At Delivery	5,123
≥ 37 Weeks Gestational Age At Delivery	16,438
Race	
White	15,156
African American	4,666
Other	1,083
Smoked cigarettes during pregnancy	3,302
Pregnancy related hypertensive disorders	
Transient hypertension	1,434
Preeclampsia mild	1,749
preeclampsia severe	962
Maternal diabetes mellitus	
Type 1	1,779
Type 2	169
Gestational	58
Inflammatory Lesions	
Chorioamnionitis	7,765
Chorioamnionitis Acute	7,715
Chorioamnionitis Chronic	25
Vasculitis	3,794
Vasculitis Acute	2,718
Vasculitis Chronic	26
Deciduitis	4,364
Deciduitis Acute	3,800
Deciduitis Chronic	606
Villitis	2,771
Villitis Acute	4
Villitis Chronic	2,745
Intervillitis	39
Intervillitis Acute	3
Intervillitis Chronic	13
Phlebitis	2
Phlebitis Acute	1
Phlebitis Chronic	0
Funisitis	2,118
Funisitis Acute	2,050
Funisitis Chronic	0
Non-Inflammatory Lesions	
Chorangiomatosis	321
Perivillous Fibrin	2694

Vasculopathy	1353
Advanced Maturation	1924
Accelerated Maturation	3
Delayed Maturation	940
Thrombosis	171
Thrombotic with Cushion	346
Stromal Vascular Karyorrhexis	57
Avascular Villi	1601
Endovasculitis	39
Intraparenchymal Hemorrhages	3
Non-Inflammatory Sub-set with Vascular Insufficiency	
Subchorionic Hematomas	6
Dysmaturity	32
Syncytial Knots	1092
Distal Villous Hypoplasia	68
Villous Agglutination	79
Chorangiosis	8
Fibrin Deposition	3288

Table 6. clinical vs. quantitative SK counts, term and preterm placenta

			Clinical Diagnosis		Quantitative SK count	
Group	Term	n	Infarct	Villious Maturation	Mean (SD)	n (%) above normal range
1	Preterm	14	-	-	23.6 (15.0)	8 (57.1)
2	Preterm	20	-	+	27.7 (17.7)	10 (50.0)
3	Preterm	7	+	-	28.3 (13.6)	4 (57.1)
4	Preterm	20	+	+	38.9 (16.0)	16 (80.0)
5	Term	15	-	-	41.6 (12.0)	10 (66.7)
6	Term	20	-	+	26.4 (13.3)	6 (30.0)
7	Term	19	+	-	38.7 (16.9)	10 (52.6)
8	Term	20	+	+	37.3 (14.6)	11 (55.0)

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__ No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X___No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics

_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X__No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, and an abbreviated title of the

publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published
2.				☐Submitted ☐Accepted ☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes____X_____ No_____

If yes, please describe your plans:

Currently the research team in Pittsburgh and Michigan are writing two papers on the data collected during this project. The papers will describe our newly developed protocol for counting syncytial knots as compared to the literature. In addition, the results from this study will be compared to the previous smei-quantitative approach evaluating syncytial knots in placenta slides used during the POUCH study, where the slides originated.

In addition, the newly developed MOMI placenta data is being evaluated for publication using an existing longitudinal cohort at Magee-Womens Hospital to investigate placenta pathology and other stress markers examined during pregnancy.

Lastly, a researcher at Magee-Womens Hospital is currently completing additional analysis on the newly available placenta characteristics within the MOMI placenta dataset. She plans to submit a manuscript on her findings in early 2014.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.
None

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.
None

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:

Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No___

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes__ No___

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

Janet Catov is a perinatal epidemiologist with extensive experience relating risk factors to pregnancy outcomes as well as long term cardio-metabolic risk. Dr. Catov is the faculty adviser to the MOMI database. She has taken an interest in placenta pathology as she continues to seek links between pregnancy complications and long term maternal risk for cardiovascular disease. Her research goal related to this project is to advance to identification of vascular pathology related to preterm delivery, in order to better understand the subset of women with preterm delivery who have excess cardiovascular disease risk. Currently, Dr. Catov and Dr. Holzman are Co-Principal Investigators on the NHLBI funded follow-up of the POUCH study mothers to link pregnancy outcomes, biologic factors including genes, and later maternal health with a particular focus on cardiovascular health.

Tony Parks' role in this project derives from his experience as a perinatal pathologist. He has been an active perinatal pathologist for the last nine years, with extensive experience in both autopsy and placental examinations. He currently examines the majority of the cases at Magee-Women's Hospital in Pittsburgh, approximately 4000 placentas and 90 autopsies per year. He has also been and continues to be the PI on several IRB-approved projects. His specific role for this project was to perform the microscopic examinations on the placental slides.

Claudia Holzman, PhD is a senior epidemiologist with a focus on maternal and child health. She has been working on methods to better characterize the maternal environment and the in-utero environment as a means of understanding social and biologic pathways leading to adverse pregnancy outcomes, particularly preterm delivery. She initiated the Pregnancy Outcomes and Community Health (POUCH) Study, which prospectively recruited 3,019 pregnant women in mid-pregnancy from 52 clinics in 5 Michigan communities (1998-2004).

Patricia Senegore's qualifications include pediatric pathology board certification (1993) and career-long interest and work in placental pathology and perinatal research. She performed clinical diagnostic work in general surgical pathology at large community hospitals in Michigan (Spectrum Health Butterworth Hospital, Grand Rapids – 1987-1990; Sparrow Heath System, Lansing 1990-1993) where she established standardized protocols for placental examination and fetal autopsy services. She worked as a placental and perinatal pathologist at the MSU Placental Registry (East Lansing MI) from 1993 until its closure in 2001, and thereafter opened a private placental pathology examination practice from 2001-2003 (Lansing MI). Since 1996 she has been involved in the MSU Department of Epidemiology POUCH Project as the sole study placental pathologist, helping to populate data in an instrument that recorded information from gross and microscopic examinations for more than 1200 placentas. She participated in the ELGAN Study (Boston MA) as a placental pathologist and served as an advisor for the in the planning stage of the MSU Department of Epidemiology ARCH Project. She has contributed as an author to many Departmental articles published that used POUCH placental pathology data.