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Official Newsletter of the

International Society for Prenatal Diagnosis

NEW AGE, INTERACTIVE ISPD A MESSAGE FROM THE PRESIDENT

The digital revolution changed our social interactions quite dramatically. An interesting example is the development of iTunes. It was 28 April 2003, only 10 years ago, that Apple started its iTunes store. It proved that consumers are willing to pay for digital downloads as long as payment is easy. The way artists release their music transformed from albums to single tracks. In fact, the consumers got a closer relationship with the artists. The expansion of iTunes with software and apps further underlines the new possibilities of interaction. This was followed soon by sites like YouTube, further bringing artists and audience together.

We are living in interesting and exciting times looking at all developments like genetic techniques and insights, noninvasive prenatal tests and imaging of the fetus and therapeutic options, ethical discussions and tools for informing the public. Our Society is really multidisciplinary and international with members from over 40 countries. This is our strength. The knowledge of prenatal diagnosis, therapy, counseling and ethics is available throughout our Society.

Therefore, ISPD is an ideal platform for discussion, questions, diffusion of knowledge, learning and forming opinions. The instruments for active interaction between all members are ready to be used. We started annual conferences, have an official journal, *Prenatal Diagnosis*, a website, social media accounts, Special Interest Groups (SIGs), the Federation of National and Regional Societies, podcasts and will introduce e-learning modules.

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All items in this newsletter are the opinions of the individual contributors and are not those of ISPD. Articles are not peer-reviewed. Additional correspondence, contrasting opinions and other comments are encouraged.

PRESIDENT'S MESSAGE

For many years the International Prenatal Screening Group (IPSG) has published a very succesful newsletter. The merger of IPSG with ISPD created the opportunity to introduce this succesful medium to our Society. The newsletter will serve to increase the interactions between the members. Our scientific work will be published in *Prenatal Diagnosis*, our day-to-day communication on our work will be via social media (twitter, facebook, linked in and others) and the newsletter is for the in between: interesting news, questions, discussions, announcements, SIG reports, membershp information, Board updates and more.

The artist working for some years on a new album, while his colleagues, friends and audience had to wait with patience, is long gone. Single tracks, or even the first notes of new melodies are quickly available for all. Developments like iTunes and YouTube made that possible. Let us as researchers, clinicians, geneticists, counselors, doctors, and related professionals follow that development. Share your knowledge, your doubts, your hypotheses, your professional emotions. Make use of all ISPD instruments; submit your scientific work for peer review to *Prenatal Diagnosis* on the one hand and make use to your own advantage of the newsletter and social media for interactive participation of all members on the other hand.

Jan van Lith

President, ISPD

Acknowledgement

Special thanks to all authors that submitted content to this Premier issue of the ISPD Newsletter, to Ms. Phillipa Bloom, Editor of Prenatal Screening Perspectives and to ISPD Headquarters staff: Allison Ball, Elliott Graham and Erin Irtenkauf.



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WELCOME!

Welcome to the Premier issue of the ISPD newsletter!

This premier issue is distributed to all ISPD colleagues free of charge. We invite you to read this issue and imagine how it will grow to serve the needs of all our colleagues working in the field. The newsletter is planned to publish quarterly and will be emailed to members as a member benefit, so we hope you will join ISPD to receive this and so many other member benefits.

We hope you enjoy reading this first issue and think of ways you can contribute content to this new ISPD communication tool! Please write back with your comments and the editors will include excerpts in the next issue.

IPSG Merges with ISPD

On 31 August 2012, the ISPD Board of Directors approved the merger of the International Prenatal Screening Group (IPSG) into the ISPD Prenatal Maternal Screening SIG. Under the agreement, ISPD now provides this newsletter. Former members of IPSG can receive the Newsletter at a low cost or they can join ISPD. Advantages to joining include the following:

- Membership in the Prenatal Maternal Screening SIG;
- Access to the ISPD member's only website, which hosts a searchable member directory, SIG information and news, and online access to the journal *Prenatal Diagnosis* (Wiley), including issues of the journal from 1981 to present;
- This ISPD quarterly newsletter, which includes a section on *Prenatal Screening Perspectives*, as well as news from other ISPD SIGs and committees;
- Reduced member rates to the ISPD 17th International Conference, to be held 2 5 June 2013 in Lisbon, Portugal.

Full details of membership and the meeting are available at www.ispdhome.org/.

ISPD Mission Statement Updated and Reaffirmed

The mission of the International Society for Prenatal Diagnosis is to:

- advance the science and evidence based practice of all aspects of prenatal diagnosis and therapy;
- foster education in and knowledge of the above areas, among members and the public, by means of international symposia, meetings, courses and the Society's journal, Prenatal Diagnosis;
- encourage the exchange of information and experience among members and between members and the public; and
- offer a platform from which a variety of relevant opinions may be disseminated to members, other professionals and the public.



International Society for Prenatal Diagnosis

2013



Join us in Lisbon for the ISPD 17th International Conference on Prenatal Diagnosis and Therapy, 2 - 5 June 2013! The event begins with a day of preconference courses organized by the ISPD SIGs. Our members have planned seven excellent courses on Sunday (read more for details) to provide

conference attendees with background information on topics that will be further explored during the conference. Conference sessions start on Monday with a debate on current controversies in the field, invited speakers and selected abstract presentations. Our Spanish and Portuguese partners, AEDP and APNDN, have organized symposia on controversies faced in Spain and about fetal brain, respectively. Meet and mingle with colleagues at the welcome reception on Monday evening. Days two and three of the conference bring even more interesting talks and cutting edge research. Visit the online program to plan your conference itinerary; full text of the selected abstracts is available. Please remember, the last day for early registration rates is 6 May 2013, so register now to save \$100!

Scientific Program Committee

Co Chairs: Alexandra Matias, MD PhD Hospital De S. João

Committee:

ISPD

Diana Bianchi, MD Mother Infant Research Institute - Tufts Medical Center

Filipa Carvalho, PhD University of Porto

Lyn Chitty, PhD Institute of Child Health

Howard Cuckle, DPhil Columbia University Medical Center

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Lucas Otaño, MD, PhD Hospital Italiano de Buenos Aires

Marta Rodriguez De Alba

Jan van Lith, MD, PhD Leiden University Medical Centre

Visit www.ispdhome.org to register!

Vincenzo Cirigliano, PhD

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ISPD Finances

The Board is diligent about fulfilling its fiduciary responsibilities to the members. At each Board meeting the Board reviews the current state of the accounts and evaluates the current state alongside the current year budget and prior history. In brief, the financial state of the society is firm, and the Board is looking into numerous ways to increase member benefits while ensuring continuing positive cash flow each year.

At the end of 2012, ISPD net assets were \$223,966. The budget for 2013 indicates possible usage of reserves in the amount of \$23,547. The Board was willing to invest 10 percent of reserves this year as it decided to begin to hold the International Conference annually beginning this year, and this newsletter was added as a new member benefit. See below for further financial details and the 2013 budget.

2013 Budgeted Revenue

Total:	545,330
Subscriptions:	19,000
Dues:	70,000
Conference Income:	456,330

2013 Budgeted Expenses

Total:	568,877
Supporting Services:	32,720
Programs:	536,157

Reserves used to balance budget:

23,547

For questions, please contact ISPD Headquarters (info@ispdhome.org) or the ISPD Treasurer, Ignatia Van den Veyver (iveyver@bcm.edu).

NAME THIS NEWSETTER WIN

ISPD is having a contest to name the newest benefit for members, the ISPD newsletter. All readers are invited to propose one or more names that would appropriately identify this newsletter with a moniker that will attract readers and represent the uniqueness of our society.

Contest rules:

- The contest is open immediately and will continue through the end of the Annual Meeting in Lisbon.
- The Board of Directors will judge and select the name from among the nominations proposed.
- If the name that is selected is submitted by more than one person, the person that submitted it first will win the prize.
- Email entries shall be submitted to info@ispdhome.org and the date stamp on the email will be used.
- Please use subject line: ISPD NL contest.
- Entries shall also be accepted at the registration desk during the Lisbon Conference.
- The prize is a 2014 membership in ISPD and a registration fee waiver for the 2014 International Conference in Brisbane.
- The prize is not transferrable.

Get creative and send in your ideas right away!

Update from the ISPD Board of Directors

The Board has been busy in the past year and has the following to report:

- 1. The merger with IPSG was approved. ISPD will offer its infrastructure and benefits to new members from IPSG.
- 2. 2013 Position Statement on Aneuploidy was approved for posting to the website, submission to *Prenatal Diagnosis* and for announcement to the full database.
- 3. Site selection for the 2015 Conference is underway, the decision will be made and announced at the June meeting in Lisbon.
- 4. The ISPD members-only website includes presentations from the 2012 Conference.
- 5. ISPD and ISUOG are co-sponsoring preconference courses at ISUOG 2013 and ISPD 2014, in Sidney and Brisbane respectively.
- 6. Position descriptions are posted to the members-only site. Members are urged to review them and then self-nominate to run for office or lead a Committee or Special Interest Group.
- 7. Policies are posted to the members-only site. Members are urged to review these to become familiar with the organizational structure and activities of ISPD.
- 8. ISPD Board meeting minutes are posted to the members-only site.
- 9. Follow ISPD on Twitter, Like ISPD on Facebook and Join ISPD on LinkedIn.
- 10. Next Board meeting is Saturday, 1 June 2013 in Lisbon, Portugal.

Brisbane or Bust – 2014!

Pull out the travel brochures and make plans to travel down under in 2014! The 2014 ISPD 18th International Conference is set for 20 - 23 July 2014 at the Brisbane Convention & Exhibition Centre. A special feature is that the meeting will be joined with the Australian Sonographers Association (ASA) meeting. A cooperative training is also being planned with ISUOG. With more than another year to plan this meeting, there will be many new developments and plans that will make this a very special meeting, and there is still time to make your



travel plans as well! Details will be provided on the website, in future issues of the newsletter and in targeted emails. Look for updates in your inbox!

For further information, contact ISPD Headquarters (info@ispdhome.org) or the Conference Co-chairs:



Dr. Jon Hyett Clinical Professor Obstetrics, Gynaecology and Neonatology, Central Clinical School jon@fetalmedicine.com

Dr. Greg Rice Deputy Director, The University of Queensland's Centre for Clinical Research g.rice@uq.edu.au

ISPD Newsletter

FEDERATION OF NATIONAL AND REGIONAL SOCIETIES

In June 2010, ISPD hosted the first meeting of the ISPD Federation of national and regional prenatal diagnosis-related societies. The objective of the ISPD Federation is to represent prenatal diagnosis, world-wide, speaking compellingly in a unified voice the message to stimulate, support and promote education, research and knowledge in the field of prenatal diagnosis. More specifically, the purposes of the Federation are to advance the art and science of all aspects of preimplantation, prenatal genetics, and congenital anomalies diagnosis, prevention, screening and treatment; foster education in and knowledge of the above areas, among members and the public, by means of international symposia, meetings and courses; encourage the exchange of information and experience among members and between members and the public; and offer a platform from which a variety of relevant opinions may be disseminated to members, other professionals and the public.

The premise of this ISPD Federation is that an interested national or regional prenatal diagnosis society may submit documentation to the ISPD Board of Directors demonstrating its eligibility and interest in becoming a Federation member. In the first phase, national prenatal diagnosis societies that qualify per the eligibility criteria may become Federation members.

See the Federation pages of the ISPD website for more information on the Federation and benefits for Federated societies, and for information about how to become a Federation member. All national/ regional societies are invited to submit information about their activities for publication in the ISPD newsletter. Following are reports from national societies.

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The Obstetrical and Gynaecological Society of Hong Kong (OGSHK)

The Obstetrical and Gynaecological Society of Hong Kong (OGSHK) was formed in 1961, and consisted of around 350 practicing obstetricians and gynaecologists in Hong Kong. OGSHK provides an important venue for continuous medical education and fraternity between its members in Hong Kong. It also provides resources for local research, scientific forums, and public health education. Our Society is an Affiliate of the International Federation of Gynecology and Obstetrics (FIGO) and a member of The Asian and Oceanic Federation of Obstetrics and Gynaecology (AOFOG).

Each year, OGSHK organizes around nine to 12 scientific meetings including an annual scientific meeting and perinatal symposium. In particular, our Society helped host the International Fetoscopy Meeting in Hong Kong in September 2011. Our Society also co-organized an international ultrasound workshop on 11-12 August 2012. *Hong Kong Journal of Gynaecology, Obstetrics and Midwifery* is our official journal and is published annually.

Italian College of Fetal Maternal Medicine

The Italian College of Fetal Maternal Medicine is a scientific, cultural, didactic and educational organization, which combines the scientific, professional and clinical interests of a number of experts in the obstetrical, prenatal and perinatal field with the purpose of promoting and encouraging clinical, educational and research activity and to be representative both at national and international levels, in the clinical environment of obstetrics, invasive prenatal diagnosis, biochemical and biophysical research methodologies in pregnancy and ultrasound.

The principal aims are:

- 1. Prenatal diagnosis
- 2. Fetal ultrasound
- 3. Cure and surgery of the pregnant woman and the foetus
- 4. Screening programs in prenatal diagnosis and foetal medicine
- 5. Medical and legal aspects regarding prenatal diagnosis

In the year 2013 several editions of courses are scheduled. In particular, the IV National Congress of the Italian College of Fetal Maternal Medicine to be held in Rome from 13 - 15 December 2013 entitled *"Fetal ultrasound and prenatal diagnosis: national legislation. Comprehension and applicability of the first guidelines written by the Ministry of Health"*

Very next courses:

- 23 May 2013 The early anomaly scan
- 20 June 2013 Doppler in fetal-maternal medicine

Associação Portuguesa de Diagnóstico Pré-natal (APDPN)

APDPN is hosting a symposium on 3 June 2013 during the ISPD 17th International Conference in Lisbon. The symposium, "What do you need to know about fetal brain?" will be chaired by Luís Mendes Graça and Nuno Montenegro and feature the following speakers and topics:

- 1. A geneticists perspective on the aetiology of prenatally detected structural brain anomalies Kini Usha
- 2. US assessment of fetal brain in the first trimester of pregnancy Teresa Loureiro
- 3. US assessment of normal fetal brain Gustavo Malinger
- 4. US assessment of abnormal fetal brain Gustavo Malinger

Asociación Española de Diagnóstico Prenatal /Spanish Society of Prenatal Diagnosis (AEDP)

AEDP is offering a symposium at the ISPD Lisbon conference on 3 June 2013. The symposium is titled, "Prenatal diagnosis in Spain: Controversies," and will be chaired by Javier Garcia-Planells. Presentations include the following:

- 1. First trimester prenatal screening Antoni Borrell, Hospital Clinic, University of Barcelona, Barcelona, Spain
- 2. The use of microarrays in prenatal diagnosis Javier Suela
- Noninvasive prenatal testing Vincenzo Cirigliano, General Lab-Labco, Barcelona, Spain

ISPD SPECIAL INTEREST GROUP (SIGs)

Fetal Therapy Chair: Dick Oepkes MD, PhD (d.oepkes@lumc.nl)

Fetal Ultrasound Chair: Antoni Borrell MD, PhD (aborrell@clinic.cat)

Laboratory Techniques Chair: Brigitte Faas, PhD (b.faas@gen.umcn.nl)

Prenatal Maternal Screening Interim Chair: Peter Benn (benn@nso1.uchc.edu)

FETAL THERAPY SIG

Preconference Course, Lisbon

Roland Devlieger, Duputy Chair of the Fetal Therapy SIG, has organized Course 4, "Fetal therapy for congenital infections and fetal hematologic conditions." The course is considered equally suitable for established obstetricians, pediatricians, fetal medicine specialists and for those who are in training.

Course Description

In this interactive course, participants will be updated by international experts on the latest developments in the area of fetal therapy. This year's course moves away from surgical treatment and focuses on the most important fetal infections (CMV and Toxoplasmosis) and haematologic conditions (RBC alloimmunisation, FNAIT and haemochromatosis). At the end of the session, participants are invited to present and discuss their own cases in brief.

Presentation Outline

- 1. RBC allo-immunisation: Treatment in early severe cases Lucas Otaño, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
- 2. Haemochromatosis: Prenatal diagnosis and neonatal treatment Enrico Lopriore, Leiden University Medical Centre, Leiden, The Netherlands
- 3. CMV: Challenges in diagnosis Luc De Catte, University Hospitals Leuven, Obstetrics and Gynecology, Leuven, Belgium
- 4. CMV: Immunoglobulings in the prevention of congenital infection
- Roland Devlieger, University Hospitals Leuven, Obstetrics and Gynecology, Leuven, Belgium 5. Parvo-B19: Prenatal diagnosis and management
- Dick Oepkes, Leiden University Medical Centre, Department of Obstetrics, Leiden, The Netherlands
- 6. Congenital Toxoplasmosis: Prenatal diagnosis and role of antibiotics? Anniek Vorsselmans, UZ Brussel, Brussels, Belgium

FETAL ULTRASOUND SIG

Preconference Courses, Lisbon

This SIG organized two courses for the upcoming Lisbon meeting. Course 2, "Ultrasound and heart abnormalities," will be chaired by SIG Deputy Chair Monique Haak. The course is considered suitable for fetal medicine specialists and Clinical Geneticists. Course 6, "Early pregnancy screening," is chaired by SIG Chair Antoni Borrell, and is a basic course targeted at maternal-fetal medicine specialists.

Course 2 Description

Ultrasound is nowadays a routine procedure in pregnancy care. The detection of fetal heart defects remains, however, a challenge. Especially defects with normal four-chamber views are missed frequently. This course focuses on the possibilities of ultrasound in screening programs, counseling after a heart defect is found and new techniques to get more out of each examination.

Presentation Outline

- 1. 20 weeks anomaly scan and heart defects: What can you detect? What can we expect? Mar Benassar, Hospital Clínic Barcelona, Barcelona, Spain
- The heart and genetic syndromes Louise Wilkins-Haug, Brigham and Women's Hospital, Maternal Fetal Medicine, Boston, Massachusetts, USA
- 3. Cardiac function: what to use and does it make a difference? Fatima Crispi, Clinic Barcelona Hospital, Barcelona, Spain
- TGA: How to diagnose, how to counsel? Monique Haak, Leiden University Medical Center, Leiden, The Netherlands
- 5. VSDs: Tips and tricks Sally Clur, Academic Medical Centre, Paediatric Cardiology, Amsterdam, The Netherlands
- 6. Ductus venosus and tricuspid flow in the screening of cardiac defects Alexandra Matias, Hospital de S. João, Porto, Portugal

Course 6 Description

Similar to first trimester Down syndrome screening, some of the most important pregnancy diseases can be predicted in the first trimester with the combined use of previous history, biochemical and ultrasound markers.

Presentation Outline

- Screening for aneuploidy (e.g. combined test, NIPT, etc.) Katia Bilardo, University Medical Center Groningen, Groningen, The Netherlands
- Screening for fetal structural abnormalities Antoni Borrell, Hospital Clinic, University of Barcelona, Barcelona, Catalonia, Spain
- 3. Screening for prematurity Ranjit Akolekar, Medway Maritime Hospital, Gillingham, Kent, United Kingdom
- 4. Screening for IUGR and preeclampsia Fatima Crispi, Clinic Barcelona Hospital, Barcelona, Catalonia, Spain
- 5. Screening for diabetes and macrosomy Ranjit Akolekar, Medway Maritime Hospital, Gillingham, Kent, United Kingdom
- 6. Early screening in multiple pregnancies Alexandra Matias, Hospital de S. João, Porto, Portugal

CGH-arrays and Fetal Anomalies

Yair J. Blumenfeld MD, Monique C. Haakk MD, PhD, Fenna AR Jansen MD, Allan Fisher MD, Anthony Odibo MD, MSCE, Antoni Borrel MD, PhD on behalf of ISPD Fetal Ultrasound SIG

The Fetal Ultrasound SIG is conducting a review of published data linking array comparative genomic hybridization (aCGH) abnormalities with specific fetal structural anomalies. The goal is to assist clinicians to determine whether aCGH is warranted as they make the diagnosis of a structural fetal anomaly, and to guide them as they counsel their patients in this setting.

Cytogenetic karyotyping of fetal chromosomes using cells obtained from amniotic fluid, chorionic villi, or umbilical cord blood is the current gold standard of prenatal genetic diagnosis. Karyotype is able to detect aneuploidy and large chromosomal rearrangements but has limited resolution (5-10 Mb), requires subjective analysis, and has a relatively slow turn-around time (approximately two weeks) largely due to the time required to culture cells prior to analysis. The yield of karyotype in the setting of fetal structural anomalies has been reported to range from 8-35% but depends largely on the type of anomaly and the presence of a single or multiple anomalies (1). Array CGH is a molecular technique that detects the presence of chromosomal imbalances within the genome at a higher resolution level. Array CGH is used clinically in the pediatric population, especially in the setting of developmental delay (2). Experience gained from postnatal cohorts has led to the extension of this diagnostic tool to prenatal diagnosis (3,4).

Despite advances in aCGH technique and several societal statements, there are no universal guidelines regarding the application of aCGH in prenatal diagnosis (5,6,7,8). In addition, questions regarding the optimal platform, as well as resolution for prenatal diagnosis remain. The yield of aCGH over a standard karyotype in the setting of prenatally diagnosed ultrasound anomalies has been reported in several studies to be 2.0-8.2%, higher than the observed yield 1.1-5.3% for overall indications. Similarly to karyotype rates seem to depend largely on the type of malformation (Table 1) and presence or absence of multiple anomalies (4,9,10,11). For example, an underlying genetic abnormality is more likely to be found when in the setting of multiple anomalies or when intrauterine growth restriction (IUGR) is present (11,12).

Study	Cardiovascular	Central Nervous System	Hydrops/ cystic hygroma/NT	Skeletal	Diaphragmatic Hernia/ Gastrointestinal	Craniofacial/ Cleft lip
Lee CN et al. BJOG 2012 3171 patients	7/50 (14%)	4/22 (18.2%)	1/17 (6.7%) increased NT	2/23 (8.7%)	1/7 (14.3%)	
Shaffer et al. Prenatal Diagnosis 2012 2858 patients	6/193 (3.1%)*	23/326 (7.1%)*	10/232 (4.3%) cystic hygroma*	15/165 (9.1%)*	1/9 (11.1%)*	3/70 (4.3%)*
Lu XY et al. Pediatrics 2008 638 patients	22/101 (21.8%)		1/13 (7.7%)	0/13 (0%)	0/11 (0%)	1/21 (4.8%)

Table 1: Yield of array CGH abnormalities in cases of prenatal structural defects

*isolated lesion within that organ system NT = Nuchal translucency

Continued...

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LABORATORY TECHNIQUES SIG

Laboratory Techniques SIG Activities

Recently, the ISPD Board approved a Position Statement developed by a Working Group, the Aneuploidy Screening Committee. Some members of the Laboratory Techniques SIG, actively involved in NIPT, were also part of this group. This updated policy document includes both conventional screening and non-invasive testing using cell-free fetal DNA in maternal plasma. Please go to www.ispdhome.org/public/position-statements.aspx to view this document.

Preconference Courses, Lisbon

The Laboratory Techniques SIG co-organized two preconference courses this year.

Course 1, "Array in prenatal diagnosis," chaired by SIG Chair Brigitte Faas, will take place in the morning, and Course 5, "Noninvasive prenatal testing," chaired by Professor Lyn Chitty, in the afternoon.

Both are meant to be basic courses, suitable for all clinicians, counselors and laboratory personnel and are designed to give the participant of the main conference background information on topics outside their specific field of expertise. The goal is to enable participants to more effectively appreciate the sessions outside their own main field of interest.

Course Descriptions

In Course 1, principles of the different platforms for array analysis will be explained (e.g., arrayCGH vs SNP array, targeted vs nontargeted array analysis, etc.). Topics such as interpretation of results and categorization of copy number variants will be covered, and participants are encouraged to actively think about dilemmas in counseling. Finally, as techniques are changing very rapidly, we will look into the future and discuss the application of next generation sequencing in prenatal diagnosis.

Presentation Outline:

- Overview of types of array and application Brigitte Faas, Radboud University Medical Centre, Department of Human Genetics, Nijmegen, The Netherlands
- Overview of current literature on use of arrays in PND John Crolla, Wessex Regional Genetics Laboratory, Salisbury District Hospital, Odstock, Salisbury, Wiltshire, UK
- Use of arrays in IUFD and miscarriage Ignatia Van den Veyver, Department of Obstetrics and Gynecology, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA
- Diagnostic dilemmas in counseling for VOUS in prenatal array analysis Ankita Patel, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA
- From array to exome or whole genome sequencing in prenatal diagnosis? Ignatia Van den Veyver, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA

Continued...

Course 5 Description

In the NIPT course, principles of the non-invasive testing for different indications will be discussed. Current applications will be explained and we will also look to the future and explore the potential of these new technologies which are currently changing the face of prenatal testing.

Presentation Outline:

- NIPT for aneuploidy Comparison of methods, laboratory performance and application Brigitte Faas, Radboud University Medical Centre, Department of Human Genetics, Nijmegen, The Netherlands
- 2. Implementation of NIPT for genetic conditions into clinical practice Lyn Chitty, UCL Institute of Child Health, London, UK
- Integration of NIPT for aneuploidy into prenatal care: What happens when the rubber meets the road?
 Diana Bianchi, Department of Pediatrics, Floating Hospital for Children, Tufts University School of Medicine, Boston, Massachusetts, USA
- Translation into clinical practice NIPT for fetal blood group antigens Dick Oepkes, Leiden University Medical Centre, Department of Obstetrics, Leiden, The Netherlands
- Noninvasive exome sequencing Ignatia Van den Veyver, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA

Please join us in one or both of the courses!

PRENATAL SCREENING SIG

Welcome to this special section of the ISPD Newsletter which incorporates *Prenatal Screening Perspectives*, the newsletter of the former International Prenatal Screening Group.

Preconference Course, Lisbon



As discussed at the Prenatal Maternal Screening SIG meeting in Miami, the theme of the preconference course run by this SIG will be **Carrier screening for single gene disorders**.

Course Description

Advances in genetic testing technology are resulting in the comprehensive and inexpensive detection of carriers for single gene disorders. Using specific examples, we will begin by reviewing and updating the progress that has been made in carrier screening in defined population groups where disease prevalence was high. We will then consider issues that are associated with emerging testing for additional common

genetic disorders. The performance of universal carrier screening that allows testing for a broad panel of gene mutations will be presented. We will conclude with a perspective on future carrier testing and the associated ethical challenges.

Presentation Outline:

- Screening for hemoglobinopathies
 C.L. Harteveld PhD, Laboratory for Diagnostic Genome analysis (LDGA) Department of Clinical Genetics, LUMC, Leiden, The Netherlands
- 2. Screening for the Ashkenazi Jewish population. Diseases, counseling, and societal issues Susan Gross, Albert Einstein College of Medicine, Bronx, New York, USA
- 3. Emerging tests: Fragile X and SMA Howard Cuckle, Columbia University Medical Center, New York, New York, USA
- Universal carrier screening Gabriel Lazarin, Counsyl Inc, South San Francisco, California, USA
- The future for carrier screening and the complex emerging ethical challenges Peter Benn, University of Connecticut Health Center, Division of Human Genetics, Farmington, Connecticut, USA

For more information on the entire ISPD meeting, visit www.ispdhome.org/2013.

SECTION 1: ESTABLISHED SCREENING

Maternal Weight

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The need to adjust first and second serum markers for maternal weight is well established. The inverse relationship between weight and concentration is not the same for each marker and the overall impact of weight inaccuracy on risk figures will depend on the combination of markers used.

Huang *et al* (1) show the effect of a five pounds (2.27 kg) error in weight for the first trimester Combined test (PAPP-A, free beta-hCG and NT with a 1:350 term cutoff). The clinical importance was most evident for women with risks close to the cut-off. For example, for women with Down syndrome risks in the range 1/250 to 1/350 (i.e. borderline screen-positive) an upward revision of five

pounds changed one-third of the risks to screen-negative. Similarly, for women with risks 1/351 to 1/400 (borderline screen-negative), a downward adjustment by five pounds changed approximately 43% to screen-positive. Even larger effects were noted for an integrated screening protocol.

Huang *et al* note that for integrated screening, the second trimester weight was not always available and that the use of the first trimester weight had a minimal effect on overall screening performance. In the next article, Howard Cuckle and David Krantz point out that the between-trimester weight gain may be a function of the initial weight and provide a basis for adjustment when the second trimester weight is not available.

Generally, it would be better to impress on the referring physician offices that this is an important factor and that they should routinely provide patient weight.

 Huang, T *et al.* The impact of maternal weight discrepancies on prenatal screening results for Down syndrome. *Prenat Diagn*. Eprint ahead of publication. DOI: 10.1002/ pd.4090

Sequential screening - extrapolating weight

Howard Cuckle (h.s.cuckle@leeds.ac.uk) David Krantz (david.krantz@perkinelmer.com)

A situation sometimes arises in sequential screening that the first trimester request form has missing information on maternal weight but a second trimester weight is available to adjust the markers in the second blood sample. Could the later weight be used to improve the risk assessment for both samples? And, the reverse situation could arise where the weight is available in the first trimester and not in the second.

One approach is to use information on the average change in weight over a given gestational period to extrapolate backwards or forwards. A PubMed search came up with a paper on this topic which has just been e-published ahead of print: Hutcheon *et al.* A weight-gain-for-gestational-age z score chart for the assessment of maternal weight gain in pregnancy (1). (*Am J Clin Nutr,* 2013 Mar 6, e-publication).

A total of 648 women were weighed sequentially an average of 10 times. The authors then tabulated various centiles of weight gain between the pre-pregnancy weight and each gestation from six weeks to term (Table 1 in the paper). The average change in weight between two gestations could be estimated from the difference in median weight gains for those weeks. For example, at 12 weeks the median weight gain is 2.3 kg and at 15 weeks it is 3.5 kg so a reasonable expectation for the weight gain between 12 and 15 weeks would be 1.2 kg. However, the spread of weight gain increases with gestation so to use this for an individual woman one would need to know the centile of weight gain up to (say) 12 weeks and the expected weight gain between gestations for such a centile. This was not tabulated, rather they show, for each gestation, the centiles of weight gain from the weight pre-pregnancy and this cannot be used to estimate the individual weight gain between gestations.

Week	Women	Centile (kg)					
		10th	25th	Median	75th	90 th	
9	271	54	57	64	72	80	
10	1066	54	58	65	72	82	
11	1523	54	59	65	72	82	
12	1400	54	59	65	75	86	
13	889	54	59	65	73	85	
14	221	55	60	67	74	85	
15	138	56	61	68	76	90	
16	89	56	61	67	79	95	

A second test would be to use cross-sectional data, that is mainly women weighed only once but at different gestations. Below is such data from Leeds Screening Centre which may be a guide:

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2013

However, we have obtained actual sequential measurements from NTLabs on about 39,000 screened at 9-13 weeks and for a second time at 15-21 weeks:

	Women -	Median weight (kg, converted from lb)				
VVEEK		First	Second	Gain	Per day	
9	1881	62.6	65.3	2.3	0.043	
10	3538	63.0	65.3	2.3	0.046	
11	7590	63.5	65.8	1.8	0.049	
12	19,247	64.4	66.2	1.8	0.054	
13	6802	66.2	68.0	1.4	0.059	

This shows that the any equation used to predict weight needs to include the gestation of the first and second measurements as well as the original weight. Also the weight gain varies according to the first weight: for women with <75th centile the median was 1.8 kg, for those in the range 75-90th centile 1.4 kg and for those exceeding the 90th centile it was only 0.9 kg.

We have used this data in a regression analysis and derived these equations (wt1&2 are the two weights in kg, ga1&2 are the two gestations in days; kg=pounds*0.453592):

wt2 = -3.789+1.018*wt1-0.04932*ga1+0.09027*ga2+0.0003103*wt1* ga1-0.0004915*wt1*ga2

wt1 = 8.205+ 0.9710*wt2 -0.07290*ga2 -0.06710*ga1+0.0005987*ga1*ga1+0.0002419* wt2*ga2

The ethnic mix in this U.S. population was 54% Caucasian, 14% Hispanic, 12% Asian, 10% African-American and 10% other. There were large differences in median weight between the groups ranging from 56.7 to 74.8 kg, but the median gain per day did not differ substantially, with range 0.049-0.054. A more detailed analysis than we have done so far would be required to determine if ethnic-specific equations are needed.

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First Trimester Serum Markers and Pregestational Diabetes

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t is well established that there is a reduction in the second trimester maternal serum concentration of AFP in women with diabetes (1). Recent data suggests that there is also a reduction in PAPP-A (2) and that the effect may be greater for Type 2 compared to Type 1 diabetes (3,4). It is possible that the extent of the PAPPA reduction could be related to diabetic control and one study did show an inverse relationship between serum PAPP-A and HBA1C (5). There is conflicting data on first trimester hCG levels in diabetic women (2-7).

- 1. Huttley W et al. (2004). Prenat Diagn, 24, 804-7.
- 2. Spencer K et al. (2010). Prenat Diagn, 30, 937-40.
- 3. Savvidou MD et al. (2012). BJOG, 119, 410-6.
- 4. Ball S et al. (2012). Fetal Diagn Ther. 31, 162-9.
- 5. Madsen H et al. (2012). Acta Obstet Gynecol Scand, 91, 57-61.
- 6. Ong CYT et al. (2000). Br J Obstet Gynaecol, 107, 1265-1270.
- 7. Lambert-Messerlian G et al. (2009). J Med Screen 16,102-3.

Multi-fetal Reduction – Are First Trimester Serum Markers Altered?

Howard Cuckle (h.s.cuckle@leeds.ac.uk)

This is not a simple question. Second trimester marker levels were reported years ago on pregnancies reduced from twins to singletons and the results are variable. To our knowledge there are no first trimester marker studies.

The situation might be similar to natural fetal demise of a co-twin where PAPP-A is raised by about 20% and hCG by a smaller amount. Most of this effect is in cases where sampling was within four weeks of the estimated time of demise where PAPP-A is increased by about 50% and hCG 33%. If this is a guide one would not use first trimester serum markers within four weeks of reduction.

There seem to be too many unknowns here and the best advice would be to rely totally on NT and other ultrasound markers. Also, if the reduced fetus had trisomy 21, one would need to increase the prior risk as if there had been a previous singleton affected pregnancy.

Vanishing Twins – Increased PAPP-A

Chasen *et al* (*Am J Obstet Gynecol* 2006;195(1):236-239) have compiled a series of 41 pregnancies where a non-viable embryo was seen at the NT scan, in addition to the viable embryo. The median maternal serum PAPP-A level was 20% higher than in more than 4000 singleton controls, an almost statistically significant elevation (P=0.06). There was a smaller increase in free ß-hCG levels (P=0.16).

Using the CRL of the non-viable embryo to estimate the time of the fetal demise, in 24 cases this was within four weeks of serum test. In these cases the differences were larger and reached statistical significance: median PAPP-A was elevated by 50% (P=0.002) and free β -hCG 33% (P=0.03).

Confounding with ART could have influenced the results since IVF had been performed in 63% of vanishing twins and only 3.3% of controls. However, logistic regression showed that there was a biochemical effect independent of ART.

MTHFR Polymorphisms

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Prenatal counseling women who are carriers of the common polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene has been highly problematic. There have been conflicting reports associating the common variants (usually designated C667T and A1298C) to thromboembolic disease, stroke, aneurysm, peripheral artery disease, migraine, hypertension, recurrent pregnancy loss, offspring with neural tube defects, some cancers, neuropsychiatric disease, and chemotherapy toxicity. Carrier rates vary considerably depending on the population but can be as high as 85%. In the past, many individuals have received the genotyping as part of the work-up for throbophilia. There are, therefore, many women seeking prenatal genetic counseling who already are aware that they, or their partner, are carriers.

Welcome guidance comes in an ACMG Practice Guideline (1). They note that MTHFR should not be part of the routine evaluation for thrombophilia because any associated hyperhomocysteinemia that may arise in carriers of the enzyme variants has not been shown to be a risk factor for cardiovascular disease. Testing is also discouraged by the American Congress of Obstetrics and Gynecology (2) and the British Society for Hematology (3).

The ACMG Guideline notes that C667T heterozygote, A1298C homozygote and the compound heterozygote genotypes are unlikely to be of clinical significance. For C667T homozygotes, measurement of homocytstine is recommended and, if elevated, they suggest there is a slight risk for venous thromboembolism (odds ratio 1.27) and recurrent pregnancy loss (odds ratio 2.7). They also recommend reviewing all risk associations for C667T homozygotes and suggest a modestly increased risk for offspring with an open neural tube defect (odds ratio 1.6). MTHFR genotype does not change the recommendation that all women of childbearing age receive folic acid supplementation.

- 1. Hickey et al. (2013). Genet Med, 15, 153-156
- 2. Lockwood & Wendel (2011). Obstet Gynecol, 118, 730-740
- 3. Baglin et al. (2010). Br J Haematol, 149, 209-220



Soft markers – How and When to Use Them

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Whilst there may be clinical utility in the ad hoc use of soft markers in. say, women with borderline screening test risks, routine use is not generally recommended. In the United Kingdom, National Fetal the Anomalv Screening Program has stated that unscreened women should "have counselling based on maternal age and/or family history not on whether normal variants are found during scannina"

(fetalanomaly.screening.nhs. uk/programmestatements#file id11216).

new meta-analysis of publications on "soft" markers of Down syndrome has been published (Agathokleous et al. Metaanalysis of second-trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013;41(3):247-61). For each marker, likelihood ratios are estimated for when it is present and when absent. The product of all LRs can then be used to modify the pre-scan risk. For example, if the prior risk is one in 100 and the scan finds an intracardiac echogenic focus, echogenic bowel but no other markers the revised risk is one in 10; if echogenic focus is the only marker seen it is one in 105 and no markers were seen one in 760.

A problem with meta-analyses of soft markers is that many of them are gualitative and the studies being combined could have used different criteria, for example in evaluating intracardiac echogenic focus or echogenic bowel. Other markers are quantitative, but they too are expressed differently from study to study. Thus, nuchal skin-fold, femur length (FL) and humerus length (HL) are often expressed in MoMs whilst nasal bone length is usually expressed as a ratio of the BPD. Moreover, even when expressed in gestation-specific terms most studies dichotomize the quantifiable markers into large or small using different criteria. Agathokleous et al have done their best to allow for these problems but it may eventually be better to carry out a single large study with strict standardized criteria. If this were to be followed by a training and accreditation, like we have for NT, this examination could be used effectively.

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SECTION 2: NATIONAL POLICIES

Contingent screening for Down syndrome – Israel

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n early January the Israel Ministry of Health wrote to all hospitals and HMOs informing them of the new national Down syndrome screening policy. All women presenting at 10-13 weeks are to be offered, as the first step, the combined markers NT, PAPP-A and free β -hCG. Those with a term risk exceeding 1:60 would be offered invasive prenatal diagnosis. Those with risks in the range 1:61-1:3000 would have risk revision after further additional second trimester serum marker testing – AFP and uE₃, with or without inhibin. The second step cut-off would be 1:380 at term.

We have modeled the policy using marker published parameters (Cuckle & Benn, 2010) and a Gaussian maternal age distribution with mean 29 and SD six years. This predicted that at the first step the detection rate would be 74% for false-positive rate 0.9%; 26% would have the second step and the total detection and false-positive rates would be 89% and 4.6% using AFP and uE_3 , or 80% and 4.0% using all three second trimester markers. Modeling also shows that the borderline group could be reduced with little impact on the total detection rate. Raising the lower limit to 1:2000 the borderline group would be 20% with no effect on detection (at least to 2 significant figures) and raising it to 1:1000 the predictions are 12% borderline with a 1% reduction in total detection rate. This loss could be recouped by lowering the upper limit to 1:200, giving 10% borderline, but the total false-positive rate would be increased 0.2-0.5% and most invasive testing would be after the first step.

The Ministry of Health also specified that women aged over 35 will be eligible for free invasive prenatal diagnosis regardless of the screening test result. If all older women took up this option the results of the contingent screening would be poorer. The first step detection rate would be 62% for false-positive rate 0.4%; 20% would have the second step and the total detection and false-positive rates would be 81% and 2.6% or 83% and 2.3%. In addition the Ministry of Health said that those with first step risks of 1:61-1:200 could consider invasive testing, which again would make the test less efficient.

Whilst giving special consideration to women aged over 35 is illogical, it is a legal requirement. To remove it legislative change would be needed, which would be cumbersome.

 Cuckle HS, Benn PA. (2010). Multianalyte Maternal Serum Screening for Chromosomal Defects. In A Milunsky & JM Milunsky (Eds.), *Genetic Disorders and the Fetus: Diagnosis, Prevention and Treatment - 6th edition* (pp 771-818.). Wiley-Blackwell Chichester.

Quality Assessment Based on Comparing Screening Performance

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In a national or regional Down syndrome screening program, is it possible to do quality assessment by comparing an individual hospital's performance with that in a sentinel hospital? This question has arisen in Sweden where health care providers would like to award financial remuneration to units according to their screening performance. We understand from Peter Conner that professionals feel results are not significantly different between units and would like to be able to specify how many women would need to be screened in order to determine a significant difference.

Let's suppose the assessed and sentinel hospitals were of (a) the same size and (b) the same maternal age distribution, with truly different detection rates of 91% and 83% respectively. To have a 50:50 chance of showing that their results were significantly different (at the level of P<0.05) they'd need to each have screened 96 Down syndrome cases. It may be more statistically powerful to compare the area under the ROC curves. If (b) was not true the only option would be to compare the areas under the curve for likelihood ratios rather than risks. This would make it even harder to show that the results were significantly different.

We would like to hear additional/alternative ideas from statistically inclined readers; if you have any ideas or thought on this please email Peter Conner (peter.conner@karolinska.se).

SECTION 3: NONINVASIVE SCREENING USING CFDNA

NIPT: Big Business

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Noninvasive prenatal testing (NIPT) using cell free DNA (cfDNA) in maternal plasma is now a billion dollar industry. Genomeweb News reported in January that Sequenom's test volume is running at 120,000 tests per year and Ariosa's run rate is 100,000 per year (1). No figure appears to be available for Verinata or Natera but the annualized rate for the U.S. must be in excess of 250,000. In a Business Wire article in January, Dr Jeffrey Bird, Executive Chairman and CEO for Verinata (now owned by Illumina) is quoted as estimating that there are approximately 500,000 high-risk pregnancies in the United States (2). There are approximately 4 million births per year in the United States.

In China, Berry Genomics expects to perform 100,000 tests this year and no figures are available for BGI (1).

- 1. http://www.genomeweb.com/sequencing/focusing-chinese-market-berry-genomicsexpects-run-100k-noninvasive-prenatal-tes
- 2. http://www.businesswire.com/news/home/20130106005112/en/Illumina-Strengthens-Leadership-Position-Reproductive-Health-Agreement

NIPT: Nomenclature

For aneuploidy screening based on the analysis of cell free nucleic acids, the use of the term "noninvasive prenatal diagnosis" is no longer being used because the testing is not fully diagnostic. The term "noninvasive prenatal testing" is preferred. When the testing is based on cell-free DNA (cfDNA) analysis, the testing can be referred to as "cfDNA screening." The component of the DNA that is conceptus-derived is popularly referred to as "fetal" although it is actually thought to be derived from trophoblasts.

"Detection rate (DR)" and "false-positive rate (FPR)" are usually used based on clinical rather than analytic validity; that is assessed based on the presence or absence of the disorder in fetuses or babies. In conventional screening, there are well established situations where there are alterations in markers (e.g. pregnancy complications, other fetal conditions) but it is not usual to exclude these cases from the overall assessment of DR and FPR. Following the same convention, cases where there are discrepancies between NIPT results and the fetal karyotype due to confined placental mosaicism or other recognizable reasons should be included in the overall measure of DR and FPR.

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NIPT: Twins

In theory, NIPT should be at least as effective in monozygotic twins as singletons. It may be better because there is a larger placental mass producing fetal DNA fragments. But in dizygotic twins that are discordant for aneuploidy, the cfDNA for the abnormal twin is diluted by both maternal DNA and cfDNA from the normal twin. Therefore, the detection rate could be lower. The only published data available is for seven discordant twin pregnancies (1,2) all of which were correctly classified. Sequenom offers NIPT for twin pregnancies but it is not clear whether an adjusted z-value cut-off or deeper sequencing is used to allow for the possibility of a poorer separation in DNA fragment counts for a discordant pair. Robust estimates for the detection rate and false positive rate, or the likelihood ratio that might be used to adjust a prior risk are not available.

For women with dizygotic twins who have received first trimester conventional screening, there will be two separate risk figures, one for each fetus. These risks figures can be quite different. If these women now receive a positive NIPT, they are presented only with information that one, or the other, or both, may be affected. For dizygotic twins, most likely only one is affected it is more likely to be the one with the higher first trimester conventional screening risk. Second trimester ultrasound may, or may not, provide some additional insight. True status can only be definitively resolved through invasive testing or evaluation at term. Counseling is complex and this is very stressful for these patients.

1. Canick JA et al. (2012). Prenat Diagn, 32:1-5

2. Lau TK et al. (2013). J Matern Fetal Neonatal Med, 26(4), 434-7.

NIPT: XXY, XXX, and XYY

Verinata, Sequenom and Natera each offer testing for sex chromosome abnormalities. In one trial, for non-mosaic XXX there were 4 cases of XXX (3 identified, 1 called monosomy X), three cases of non-mosaic XXY (two identified, one unclassified) and three cases of non-mosaic XYY (all identified) (1). In another trial, two cases of XYY were identified (2). In a third trial (3), combining training and blinded validation cohorts, there were 6 cases of XXX (5 detected, 1 unclassified), 13 cases of XXY (11 detected and 2 unclassified), and 4 cases of XYY (3 detected and 1 unclassified). There was just 1 (0.05%) false-positive (XXX) among the 1922 samples without a sex chromosome abnormality but also 13 (0.67%) normal cases where gender was misidentified. It should not be assumed that the detection rates and false-positive rates for each of these three sex chromosome abnormalities will necessarily be equivalent to the autosomal trisomies. But even if NIPT efficacy was found to equivalent, the a priori risk for one of these three karyotypes is generally low and therefore the post test odds of being affected (or positive predictive value) will usually be low (4), meaning that many positives could be false positives.

For all three of these sex chromosome abnormalities, no abnormal ultrasound findings are expected. Prenatal confirmation of a positive NIPT result would therefore be entirely dependent on an invasive test. Confirmatory invasive testing is a difficult decision for women because it now requires taking the usual 0.5-1% risk for a loss but with the goal of establishing the presence or absence of a relatively mild disorder. And, it is being precipitated by an NIPT result for which there is considerable uncertainty about the accuracy

- 1. Bianchi DW et al. (2012). Obstet Gyneco, 119, 890-901
- 2. Zimmermann B et al. (2012). Prenat Diagn, 32, 1233-41
- 3. Mazloom AR et al. (2013). Prenat Diagn, Accepted manuscript.
- 4. Benn et al. (2012). Ultrasound in Obstet Gynecol, 39,127-130

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NIPT: Fetal fraction

Low fetal cfDNA fraction seems to be the most common reason for a NIPT test failure. A low fetal fraction could also increase the chance of a false-positive or false-negative result because the number of fetal fragments counted is lower and the z-score will be lower. The percentage of fetal DNA is lower for heavier women, presumably because of a dilution effect.

The fetal fraction can be considered analogous to the number of cells counted in invasive testing. In many locations, there are required standards for the number of cells counted and the cell count provides some measure of confidence that a result is accurate. In the United States, it is a requirement to provide the number of cell counts on amniocentesis and CVS reports. There is no minimum standard for the fetal fraction and the information is not provided on NIPT reports.



Low fetal fraction is not the only reason for a false-positive or false-negative NIPT result. However, routinely providing the percentage fetal DNA and also the z-score would be helpful especially for heavier women where there may be an added concern about the reliability of the result.

Laboratories providing NIPT are invited to comment on this recommendation.

SECTION 4: EMERGING SCREENING

Screening for Fragile X Syndrome – Adults or Newborns

Howard Cuckle (h.s.cuckle@leeds.ac.uk)

There is a certain screening test with excellent performance characteristics: a detection rate close to 100%, a false-positive rate of about 0.4% and odds of being affected given a positive result of 1:5. The disorder being screened for is serious, and reasonably common, and the cost per affected case detected is not great. Nevertheless in only one country is there a national screening program based on the test and in most of the developed world it is not even available. The test is prenatal or pre-conception screening for fragile X syndrome (FRS).

Why? Counseling issues have been put forward as a reason for not offering this test. Prenatal screening leads to the identification, in addition to affected male fetuses, of female fetuses with full mutations, some of whom would be expected to be unaffected. It also leads to the identification of male fetuses with pre-mutations (PMs) who are at risk of FX Tremor and Ataxia Syndrome in late middle age. Both pre-pregnancy and prenatal screening will identify adult females who are at risk of FX Premature Ovarian Failure.

Another incidental finding when screening among adult females for FRX is 47,XXX. Sharony *et al* (1) report 25 women with three peaks following PCR on their X chromosomes among 34,500 having prenatal screening for FXS. Of the 16 on whom karyotyping was subsequently performed three had complete and two mosaic (low level) triple X syndrome. For two women with normal karyotypes, their parents were karyotyped and also found to be normal.

An alternative approach is newborn screening. A study has just been published reporting the results of screening 14,207 newborns in the United States using blood spots (2). A total of 50 newborn PM carriers were identified and one affected male. No information is given on the uptake rate or s taken for the carriers although mention is made of 'cascade' screening in the fan which identified 16 additional carriers, including a great grandmother with probab

To find out more about fragile X carrier screening join us in Course 7 at the ISPD 17th International Conference, on 2 June 2013 in Lisbon, Portugal

identified and one affected male. No information is given on the uptake rate or subsequent actions taken for the carriers although mention is made of 'cascade' screening in the family of one carrier which identified 16 additional carriers, including a great grandmother with probable FX Tremor and Ataxia Syndrome, several great aunts with neurological problems and others with emotional difficulties. It sounds like this approach is also complicated by the type of counseling issues that affect pre-conception and prenatal screening.

A survey in Australia indicated that newborn screening would be acceptable (3). Out of 2094 parents offered the test 1972 (94%) accepted testing and almost all elected to be informed of both PM and full mutation results. In a questionnaire little concern was expressed about identification of infants with associated adult-onset disorders.

If there was an effective treatment for FXS it would boost the relative value of newborn versus adult screening. The latest report on this aspect is a randomized clinical trial among 63 affected children and adults of STX209, a γ -aminobutyric acid type B agonist (4). The study tended to confirm animal research suggesting that neuro-behavioural function might improve.

- 1. Sharony et al. (2012). J Med Screen, 19(3), 112-5
- 2. Tassone et al. (2012). Genome Med, 4(12):100 [Epub ahead of print]
- 3. Christie et al. (2013). Am J Med Genet A, 161A(2), 301-11
- 4. Berry-Kravis et al. (2012). Sci Transl Med, 4,152ra127

Universal Carrier Screening

Peter Benn (benn@nso1.uchc.edu)

Carrier screening for single gene disorders with a Mendelian pattern of inheritance has traditionally involved focusing on those disorders that have a high prevalence in specific populations and looking for a sub-set of the most common mutations. Advances in technology have reduced the cost of mutation detection which allows the detection of carriers in low risk populations and also facilitates the detection of rare mutations.

For example, Counsyl Inc, provides screening for 108 disorders including ACOG and/or ACMG recommended testing for cystic fibrosis, disorders that were common in the Ashkenazi Jewish population, and spinal muscular atrophy. Results have now been published for 23,453 individual screened (Lazarin *et al. Genet Med* 2013:15(3):178–186). Twenty four percent of individuals were positive for at least one condition; based on self-reported ethnicity, this frequency ranged from 43.6% of Ashkenazi Jewish individuals to 8.5% of East Asians. There were 433 individuals who were identified as carriers that would not have been recognized using traditional carrier screening criteria. This included identification of many carriers of the diseases mostly found in Jewish populations among individuals who had self-identified themselves as non-Jewish. The study demonstrated the practicality of the approach for the US population.

Gabriel Lazarin from Counsyl will present more details in the preconference course, Carrier screening for single gene disorders on 2 June 2013 in Lisbon, Portugal

Screening Spontaneous Abortion Tissues

Peter Benn (benn@nso1.uchc.edu)

Chromosome analysis of spontaneous abortion tissues and stillbirths can provide an explanation for fetal/neonatal loss and, potentially, information about recurrence risks. The yield of informative results is greater when microarrays are used but the latter testing also provides information that may not be sought; i.e. the presence of copy number variants that may have unknown or uncertain clinical significance (1,2).

Xie *et al* (3) suggest another approach. Using sequencing, they analyzed 40 aneuploid spontaneous abortion tissues and correctly identified the abnormality in all cases. The method only required a low number of unique copy reads (average 115,000/case), was performed rapidly, and at low cost.

The approach raises the possibility of routinely testing many more losses than are currently referred to cytogenetic laboratories. Presumably, the method could be refined to look for partial imbalances and thereby lead to the identification of balanced translocation carrier parents (who would be at high risk for recurrent loss and liveborns with chromosome imbalances).

- 1. Reddy et al. (2012). Prenat Diagn, 32:371-5
- 2. Reddy et al. (2012). New Engl J Med, 367, 2185-93
- 3. Xie et al. (2013). Prenat Diagn, 33, 232-7

SECTION 5: ELSI

Accreditation – creditable, but is it credible?

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The European Accreditation Council for Continuing Medical Education (EACCME), part of the European Union of Medical Specialists (UEMS), provides an accreditation system applicable throughout Europe for live educational events (LEEs), or conferences to those unfortunate enough to be abbreviation challenged. It also has mutual recognition agreements with the United States and Canada. One leg of the accreditation process is "transparency as regards funding." For example, for the upcoming ISPD Conference in Lisbon to be accredited all members of the ISPD Program Committee needed to complete disclosure forms. At many international meetings it is now mandatory for each speaker to make disclosures on a slide in any live presentation.

All this begs the question: does transparency *per se* lead to unbiased presentation of research findings? This might become a whole research field in itself. Perhaps it already exists. If so, a meta-problem will arise, which is not new but was encapsulated by the Roman poet Juvenal in the pithy quote "Quis custodiet ipsos custodes?" or "Who will guard the guardians?" although he had in mind marital fidelity rather than scientific bias.

These thoughts came to mind when I read the opinion on cfDNA screening for aneuploidy from the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC), which was recently published (1). In a preamble it was stated that disclosure statements have been received from all members of the committee. I asked the editor of *J Obstet Gynaecol Can* if these were in the public domain. He replied that Clinical Practice Guidelines and Committee Opinions published in JOGC are developed under the auspices of the Society of Obstetricians and Gynaecologists of Canada, and consequently are outside my editorial responsibilities but kindly passed my inquiry to the Clinical Publications Officer of SOGC. He promptly replied that four committee members had made disclosures of interests including a commercial cfDNA provider, Sequenom Inc.

After all this, does it help the reader to judge the veracity of a scientific paper or opinion article to know that one or more author has financial interests? No one would suggest that science can progress without involving the private sector and it can be argued that having links with industry is a measure of success for an academic department and a measure of high regard for the individual investigator. Perhaps we should rely on the integrity and reputation for quality of a presenter at a scientific meeting rather than reading the fine print of his or her financial interests.

 SOGC Committee, (2013). Current Status in Non-Invasive Prenatal Detection of Down Syndrome, Trisomy 18, and Trisomy 13 Using Cell-Free DNA in Maternal Plasma, *J Obstet Gynaecol Can*, 35(2), 177-181

Birth Defects Malpractice Suits: Israel Supreme Court

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n Israel, the number of medical malpractice suits has doubled in the past decade, but obstetrics related suits have quadrupled. Most of these relate to birth defects.

Recently, the Supreme Court has ruled that persons with birth defects *themselves* can no longer sue doctors and healthcare institutions for "wrongful birth" if they were born with a defect that could have been detected on prenatal testing. Their parents will still be allowed to seek compensation to cover the extra expenses of raising a disabled child and meeting their lifetime needs. However, this requires a causal relationship to be established between the defect that was not identified and the disability suffered. The Court endorsed the position of the Israel Medical Association that a causal relationship means that had the defect been known, an abortion committee would have agreed to termination. Therefore, the parents would be required to establish that, if not for the negligence, they would have actually applied to the abortion committee. Even if that could not be proved they can still sue for the damage done to their autonomy, if they were not provided with adequate information, the result of which a disabled child was born. This ruling should have the effect of limiting suits to serious conditions.

The justices also called on the government to adopt the recommendations of a Justice Ministry panel for no-fault compensation for damage caused by birth defects without having to prove medical malpractice. A bill to this effect is to be submitted to the Ministerial Committee for Legislation shortly but is likely to face opposition, particularly from lawyers' lobby.



SECTION 6: ASK PRENATAL SCREENING PERSPECTIVES

Not Black and White

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What race correction should be applied in prenatal screening when a woman has one parent Caucasian and one parent Afro-American or Afro-Caribbean (black)?

In Afro-American women, first trimester PAPPA is approximately 35% higher, second trimester AFP is approximately 10-15% higher, and there are also smaller differences for the other serum markers. It is, therefore, common practice to use race/ethnicity specific medians or to apply a correction factor to allow for these differences. The finding of differences in concentrations is based on women's self reporting of race/ethnicity which can be inaccurate. The biological basis for the differences is unknown. We are not aware of any studies that have looked at concentrations for pregnant women with well defined combinations of mixed race/ethnicity parentage. Although mixed ancestry is common, it is usual to base results on a single maternal race/ethnicity assignment.

For any particular woman, applying the correction factors for Black patients generally increases the reported risk for fetal Down syndrome. But applying this adjustment also means that a case with an open neural tube defect is more likely to be reported as screen-negative. Providers of testing can therefore find themselves in a "Catch-22" situation in which they can be held accountable for missing either a Down syndrome or ONTD affected pregnancy through use of the "wrong" race/ethnicity.

Patients should be asked to assign their own race/ethnicity. Physicians, counselors and others do need to be aware that incorrect assignment can have a significant impact on interpretation. Re-calculation with the alternative race/ ethnicity may be appropriate and a second trimester ultrasound exam looking for the presence or absence of fetal anomalies may sometimes also help resolve two conflicting screening results.

Who Do You Think You Are?

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Self-described ethnicity can often be misleading, simply because individuals are not always aware of their family history. But in countries where there has been severe racial discrimination in the past and where the specific racial admixture of an individual affected had legal status, as in the United States, it can be even more so.

Today molecular biology can be used to investigate the correlation between self-reported and actual ethnicity. In a study of 1,071 unrelated Americans. Halder et al. (Hum Mutat 2009;30(9):1299-309) did this with a panel of 36 microsatellites and one SNP. They found that the admixture among self-described African-Americans was 75% African, 17% European and 8% Indigenous. Those describing themselves as European-Americans were 6% African, 84% European and 10% Indigenous. For self-described Hispanics the admixture was 22%, 59% and 19% if they were from the East Coast and 11%, 53% and 36% from the West Coast.

Maternal Down Syndrome

Peter Benn (benn@nso1.uchc.edu)

What should we expect in screening a pregnancy when a woman herself has Down syndrome?

Women with Down syndrome have reduced fertility but pregnancies do occur and the risk for an affected pregnancy is very high. Sheridan *et al* (1) reviewed data for 29 pregnancies which resulted in 10 offspring with Down syndrome, two spontaneous abortions and 18 chromosomally normal offspring. Livebirth risk is, therefore, approximately 10/27 (37%). I am unaware of any data to indicate whether the serum or ultrasound markers would differ from those present in the pregnancies of unaffected women. So, presumably this 37% risk figure could be cautiously modified based on the screening results.

NIPT in such a case is likely to be problematic. Similar to a case report of a woman with a nonmosaic 46,XXX karyotype (2), the trisomy could potentially be misinterpreted as being fetal in origin or mask the true fetal chromosome copy number. And there is also the challenge of cases where there is maternal mosaicism. Low level maternal trisomy 21 mosaicism can be clinically unrecognized and could therefore potentially give a false-positive NIPT test.

- 1. Sheridan et al. J Med Genet 989;26:294-8.
- 2. Yao et al. (2012). Prenat Diagn, 32, 114-6.

False Negative CVS

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Could a CVS give a false-negative Down syndrome result?

Apparently, screening yielded a 1:5 risk, a CVS was carried out and the result was negative for Down syndrome and 'other chromosome disorders'. Subsequently, the infant, a boy has had eczema/dermatitis and a milk allergy. It would appear that there were also some features of Down syndrome and, according to the mother, a pediatrician has decided to carry out another test for Down syndrome which will take nearly two months to complete. In her own words against "...better judgment, I've been looking on the internet and reading about mosaic Down syndrome."

Opinion: A case of mosaic Down syndrome could be missed in a CVS analysis. There are also examples of babies that display many of the features of Down syndrome but show a normal karyotype. Some of these could have trisomy for a Down syndrome critical region of chromosome 21 which is too small to detect by conventional cytogenetic analysis (but might be picked up by microarray testing) or there may be a set of features that mimic Down syndrome but are not true Down syndrome. The result of the CVS should also be reviewed to check whether it specified male; maternal cell contamination can be another cause of a false-negative result but the CVS report would then have indicated a female. So, a false-negative result for Down syndrome through a CVS analysis is extremely rare but it can occur for various reasons.

The time being taken to obtain a result (or to communicate with the family) is unacceptable; it is unfair to provide no information for two months. Typically a chromosome analysis for a blood sample should only take about one to two weeks. It is possible that the lab is pursuing some additional analysis as noted above. But the paediatrician should be able to obtain a partial result or an explanation for the delay. The mother may also be able to find out the name of the lab that is providing the testing and get a direct explanation for the delay. Referral of a fresh sample to another lab might also be an option if a timely result cannot be obtained any other way (but this might incur some additional costs).

PHOTOS AND ANNOUNCEMENTS



Peter Schielen and Bent Norgaard-Pederson at the 8th ISNS European Neonatal Screening Regional Meeting. 4-6 November 2012 in Budapest. While Bent has a long history both in neonatal as well as in prenatal screening, Peter is only a freshman in neonatal, only recently succeeding Gerard Loeber as head of the reference laboratory for pre- and neonatal screening in the Netherlands. The photo could be a representation of how the fields of pre- and neonatal sceening may fuse in the next coming years.

Left to right: Peter Benn, Brigitte Faas, Howard Cuckle, and Giandomenico Palka, Chieti, Italy, July 2012. The Chieti Congress is a regional meeting and was arranged in part through ISPD's educational outreach.





23rd World Congress on Ultrasound in Obstetrics and Gynecology incorporating ASUM 43rd Annual Scientific Meeting; 6-9 October 2013

Sydney Convention and Exhibition Centre, Sydney, Australia

6 May 2013 - Abstract submission deadline 6 August 2013 - Early Bird registration deadline

Website: http://www.isuog.org/WorldCongress/2013 Contact: congress@isuog.org

Ethics of prenatal screening: brief report of a successful symposium

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At the shores of lake Geneva, in the well-facilitated conference building of the Brocher Foundation, a 1,5 day symposium was held on the ethics of new developments in prenatal screening (4 - 5 April 2013). This concerned several scenarios in which non-invasive prenatal testing (NIPT) may replace different parts (or eventually the whole) of the present screening trajectory for fetal aneuploidies, as well as the clear tendency to broaden the scope of (follow-up) testing by using micro-arrays, eventually perhaps to be superseded by whole exome or genome sequencing based testing.

These developments and scenarios raise important questions regarding the normative (ethical, legal) framework for screening for fetal anomalies. For instance, in response to the so called

"disability rights critique" (maintaining that the offer of prenatal testing for conditions such as Down syndrome reflects a discriminatory attitude towards people with mental disabilities), it has often been stressed in official documents and statements that such testing should not be understood as aimed at preventing as many children with Down syndrome as possible, but rather as promoting the reproductive autonomy of individual couples. Taken seriously, this means that the introduction of a new test should not just be evaluated in terms of its better test characteristics, but also in terms how it would affect this aim. In this connection, one concern that has been raised about the prospect of NIPT as allowing "early, easy and safe" aneuploidy testing, is that it might lead to a "routinization" that would be ill at ease with promoting



Left to right: Wybo Dondorp, Jan van Lith and Guido de Wert at the shores of 'Lac Leman' Geneva at the symposium on 'Individual Choices in Prenatal Screening'

autonomous decision making by pregnant women and their partners. Moreover, scenarios of (considerably) broadening the scope of testing raise questions about the feasibility of meaningful informed decision making: would offering an extended range of choices serve or undermine reproductive autonomy? If the notion of "maximizing" autonomous choice is inherently problematic, because it would lead to information overload and less well-considered choices, it seems that the classical aim of prenatal screening requires qualification. If, inevitably, the question arises for what conditions prenatal testing should be offered, then who should decide about this and on the basis of what criteria? These are only some of the issues that emerged at the well-attended symposium.

The meeting was organized by researchers at the Health, Ethics & Society department of Maastricht University, the Netherlands, as part of the PhD project of Mrs. Antina de Jong (supervisors: Professor Guido de Wert and Dr. Wybo Dondorp, Bioethics, Maastricht, and Professor Jan van Lith, Gynaecology, Leiden). Invited speakers were Professor Lyn Chitty (Genetics and Fetal Medicine, UK), Dr. Idit Maya (Clinical Genetics, Israel), Professor Martina Cornel (Community Genetics, the Netherlands), Professor Jenny Hewison (Psychology of Health Care, UK), Professor Christian Munthe (Practical Philosophy, Sweden), Professor Stephen Wilkinson (Bioethics, UK), Antina de Jong MA, LLM (Bioethics, the Netherlands). The meeting was attented by a further 30 interested professionals from a broad range of disciplines and a large number countries, including Argentina and the USA. The general feeling was that the symposium timely addressed important questions and that ideally this meeting should not be a one off event but the starting point of a longer term multidisciplinary endeavour, perhaps in the form of a SIG of ISPD. Planned publications based on the meeting include a paper to be submitted to *Prenatal Diagnosis* and a special issue of *Bioethics*. Those interested in receiving the scientific report of the meeting can email w.dondorp@maastrichtuniversity.nl.

Training Courses in Goldrain, Italy

An advanced training course on Clinical Cytogenetics is planned for 24-30 August 2013, at Goldrain Castle, Italy. The course is part of the European Cytogeneticists Association's education activities and are under the direction of Professor Albert Schinzel (Zurich). Faculty includes leading experts in clinical and diagnostic laboratory cytogenetics, molecular cytogenetics, and obstetrics. Topics include disease mechanisms and basic principles, test indications, diagnostic methods, interpreting complex results, reporting, database resources, discussions on ethical issues and reporting of tricky cases. A half-day is assigned to a recreational activity which can include a visit to a local cultural attraction and/or hiking. Accepted students generally have at least one year of relevant experience. This is an outstanding learning opportunity in a spectacular setting. More information is available at www.goldrain.ch/index.php. The preliminary program for the 2013 course is expected to be posted on the website shortly.

A second course on Prenatal Screening and Diagnosis may be offered on 14 -21 October 2013 also at Goldrain. This is subject to sufficient enrollment. Please contact Professor Schinzel (schinzel@medgen.uzh.ch) if you are interested in this course.

James FX Egan, MD

James FX Egan died on 19 March 2012. Jim was a graduate of the College of the Holy Cross and Georgetown University School of Medicine, and completed his OB/GYN residency at Yale University School of Medicine. After practicing general OB/GYN medicine for many years in the Springfield, Massachusetts, area, he embarked upon a fellowship in Maternal-Fetal Medicine at the University of Connecticut (UConn) School of Medicine. After completing his fellowship, Dr. Egan joined the UConn faculty in the Division of Maternal-Fetal Medicine in 1989, working as director of Maternal-Fetal Medicine and Fetal Echocardiography at St. Francis Hospital and Medical Center. He was chairman of the Department of Obstetrics and Gynecology at UConn from 2004 to 2010.

Jim's many clinical and research interests were in the areas of antenatal diagnosis, obstetrical ultrasound, fetal echocardiography, Down syndrome screening, prematurity and high risk obstetrics. He pioneered the use of second trimester ultrasound markers as a screening test for Down syndrome. He collaborated closely with colleagues and researchers and was often quoted in news stories related to maternal-fetal issues. He published extensively in obstetrics journals, *Prenatal Diagnosis*, and was a regular contributor to *Down's Screening News/ Prenatal Screening Perspectives*.

Jim had a passion for his work that was quite remarkable. His quiet enthusiasm consistently inspired not only his fellows and students, but touched all who collaborated with him. Perhaps most inspiring was his ability to accept adversity and keep fighting. This spirit was most apparent in dealing with his progressively debilitating disorder, ALS.

Jim had many interests outside of work. He loved sailing, photography and had an avid interest in American history. But his greatest joy came from his family and in particular his eight grandchildren and 12 nieces and nephews.