1. INTRODUCTION TO IGENOMIX

1.1 IGENOMIX Background

IGENOMIX is a company that provides advanced services in reproductive genetics. Our broad experience and qualifications make us one of the global leaders in this field, offering effective solutions to various infertility and genetic disease problems.

Our Mission: To increase pregnancy success ratios to deliver healthy babies through high-quality services.

Worldwide, IGENOMIX has developed a range of innovative diagnostic techniques performed in its own laboratories that significantly increases the success rate of clinician and patient satisfaction.

IGENOMIX has been providing genetic laboratory services to IVF clinics for more than 18 years.

IGENOMIX is strongly committed to research, development and innovation as a means of providing the best and latest services to its clients. The constant efforts we make in R&D enable us to create and develop specific tools to support professionals in reproductive medicine.

Figure 1: IGENOMIX laboratories in Spain

1.2 IGENOMIX origin belongs to IVI Group

IGENOMIX was founded in 1998 as the genetic laboratory of IVI Group.

The Valencian Infertility Institute (IVI Group) was founded in 1990 as the first medical institute in Spain purely dedicated to assisted reproduction. Today it is a
world leader both in the scientific community and for all couples unable to have children without assistance.

With 32 clinics across Spain, Argentina, Brazil, Chile, Mexico, Panama, Portugal, and India, IVI has secured its position as a pioneer in internationalizing medical professionalism.

As of 2008, IGENOMIX commenced its own international expansion within more than four continents and started to provide genetic laboratory services to all the IVF clinics.

1.3 IGENOMIX international presence and IVF Labs Clinical reference

Currently the company runs operations in more than 15 countries, through seven laboratories located in the key markets that allow us to offer the best services worldwide.

Figure 2: IGENOMIX laboratories location worldwide

Europe: one (1) Head Quarter and laboratory located in Valencia, Spain and one (1) laboratory in Milan, Italy.

Top IVF labs Reference in Europe: Carefertility (Uk), Pam fertility (Germany), Aava kampii (Finland), Oak clinic (Japan)

North America: two (2) laboratories located in Miami and Los Angeles, USA.

Top IVF labs Reference: Shady Grove Fertility Center (Rockville, MD), Boston IVF (Waltham), HRC Fertility (Pasarela, CA), Stanford Fertility Clínica (Palo Alto, CA), Fertility Center of Illinois (Chicago, IL), Main Line Fertility Center (Bryn Mawr, PA), South Florida Institute for Reproductive Medicine (Miami, FL)
Asia: one (1) laboratory located in Delhi, India
Top IVF labs Reference: NOVA-IVI (Bangalore), Gam Garam Hospital (Delhi), GG Hospital (Chennai).

Middle East: one (1) laboratory located in Dubai, UAE.
Top IVF labs Reference: Gov. Hamad Medical Corporation (Qatar), Gov. Jahra Hospital (Kuwait), Bourn Hall (UAE), IVF Jordan Hospital (Jordan)

Latham: one (1) laboratory in Sao Paolo, Brazil.
Top IVF lab Reference: Huntington (Sao Paulo), Origen BH (Belo Horizonte), Fertilitat (Porto Alegre)

Figure 3: IGENOMIX laboratories of PGD in Spain

Figure 4: IGENOMIX UAE Entrance in Dubai Health Care City
Figure 5: IGENOMIX UAE POST PCR Laboratory (Scanner for PGD with Sanger techn.)
2. **IGENOMIX EXPERIENCED AND INTERNATIONAL TEAM**

Currently the company has more than 150 employees (approximately 15% are senior Phd), high qualification experts supporting the work of reproductive medicine professionals.

2.1 **Board Directors**

**Carlos Simón M.D., PhD, Chief Scientist Officer (C.S.O.)**

Board Certified and Full Professor of Obstetrics and Gynecology at the University of Valencia; Adjunct Clinical Professor, Department of Ob/Gyn, Stanford University School of Medicine, CA; Scientific Director of Instituto Valenciano de Infertilitad (IVI) and IGENOMIX.

Since 1991, his basic and clinical research has contributed to the advance of Reproductive Medicine, specifically in the understanding of human endometrial receptivity, embryo viability, embryonic implantation and endometriosis. He discovered the relevance of the interleukin-1 system in embryonic implantation (Simon et al., JCEM 1993; 1994; Endocrinology 1994; BOR 2006). He demonstrated the deleterious effect of high hormonal levels in patients with high response to gonadotrophins thus modifying the established clinical practice (HR1995; Fertil Steril 1996; 1998). He pioneered the concept that human oocytes are affected in endometriosis (HR 1994; Fertil Steril 2000) thus changing the clinical practice in oocyte donation. He proposed a new embryo coculture system, now successfully used worldwide (JCEM 1996; Fertil Steril 2003). His basic research on endometrial receptivity led him to create and patent a customized array named endometrial receptivity array (ERA) for the molecular diagnosis of endometriosis (Fertil Steril 2011, 2013). He has been awarded “Prize Jaime I 2011 in Medical Investigation” for his pioneering work in human endometrial receptivity disorders.

**David Jiménez, Chief Executive Officer (C.E.O.)**

David earned a major in Business Science and an MBA from ESADE Business School. He is specialized in International Finance, with over 15 years of experience in consumer goods industries and 5 years in the health care industry. He has developed most of his career internationally, both in Europe and in America, working in Switzerland, US, Mexico and Spain. He is an executive with broad private and public company backgrounds in both emerging and Fortune 500 companies. During his career, he has hold different responsibilities in Marketing, Finance, Business Development and IT providing him a wide view of business. David has been in general management for the last 6 years. He speaks fluent Spanish, English and French.
2.2 Scientific Professionals and Laboratory Teams

Carmen Rubio, PhD Lab Director PGS Molecular Cytogenetic

Trained in science in the University of Valencia, Spain, Dr Carmen Rubio specialized in cytogenetic studies in human reproduction, partly in the University of Barcelona.

Becoming interested in chromosomal abnormalities in human embryos, she completed her PhD in 2004 in Valencia in the field of Reproductive Genetics. Post-doctoral research includes a sabbatical at the laboratory of Drs. Patricia Hunt and Terry Hassold at the School of Molecular Biosciences (Washington State University, USA) focused in male and female meiosis and the mechanism underlying human aneuploidy. At present, she is the Head of the Preimplantation Genetic Diagnosis program for chromosomal disorders at IGENOMIX (Valencia, Spain).

She has published more than 100 papers in the main peer-reviewed specialist journals in the field, books chapters as well as numerous lectures at conferences worldwide. She is one of the most cited authors in the field, with more than 20 year professional experience. She is Professor of the Master in Biotechnology from the University of Valencia.

Julio Martín, PhD Director Carrier Genetic Test and Molecular Genetics

Julio Martín completed his undergraduate in Biology in 1995 at the University of Barcelona (UB). He obtained a Master’s degree in Biotechnology in 1997 (UB, and Polytechnic University of Catalonia).

In 1998 he held a predoctoral research fellowship in the Department of Ob./Gyn., School of Medicine (University of Valencia) joining the group of Professor Carlos Simon at IVI foundation.

In 2002 he specialized in molecular genetics for in vitro embryo diagnosis at the Centre for Medical Genetics (UZ-Vrije Universiteit Brussel) joining the group of Dr. Sermon and Dr. De Rycke, directed by Professor Inge Liebaers. He has been director of the Laboratory of Molecular Diagnosis, (Preimplantation Genetic Diagnosis Unit) in the University Institute IVI Valencia since 2003.

Currently working in IGENOMIX as a Head of the CGT and molecular diagnosis department. His main interest is in the field of genetics of single-gene disorders and applied molecular technology to in vitro embryo diagnosis and non-invasive prenatal diagnosis.

Ana Cerveró, PhD Lab Director PGD Molecular Genetics

Ana Cervero received her Bachelor degree and her Ph.D. in Biochemistry at Valencia University (Spain).
In her research for the Ph.D., Ana Cervero was focused in human endometrial receptivity. Ana Cervero has over 7 years of clinical laboratory experience, first at IVI-Valencia Clinic (Spain) at the Preimplantation Genetic Diagnostic Laboratory and then at IGENOMIX (Spain) as a lab manager at the monogenic PGD and Molecular Diagnosis Department. In her research, Ana Cervero has been published in scientific journals including JCEM, Endocrinology, Molecular Human Reproduction and Fertility and Sterility.

David Blesa, PhD Head of Product Development

David Blesa is Doctor in Biological Sciences by the Department of Genetics at the University of Valencia in Spain. Currently Dr. Blesa is the Head of the Product Development Department at IGENOMIX. From 2011 until 2013 he has been Head of Research & Development at the IVI Foundation and also Head of the Product Development Department at IGENOMIX S.L.

From 2006 to 2011 he was Researcher and Head of the Genomics Core Facility at the ‘Principe Felipe Research Centre’ (CIPF) in Valencia, Spain. Previously, since 2000, he worked in the field of cancer genetics first as Postdoctoral Fellow at the ‘Hospital Clínico Universitario’ in Valencia and at the ‘Spanish National Cancer Research Centre’ (CNIO) in Madrid and later as a Researcher at the CNIO within the Molecular Cytogenetics Group until 2006.

His main interest is centered in the field of genetics and genomics of human health and specifically in reproductive health. He has been principal researcher in projects financed by the Valencian and the Spanish Science and Innovation Governmental Office and is author in more than 25 research papers published in international journals and author in several book chapters.

Mª Eugenia Póo, Embryology Director PGD Molecular Genetics & Cytogenetic

María Eugenia Póo received her Bachelor’s degree in Biology at the Simón Bolivar University (USB), Caracas, Venezuela and completed training in immunology of human reproduction and molecular biology through postgraduate courses at the same university and the International Institute of Advanced Studies (IDEA).

Póo has worked in the human reproduction field for more than 12 years in Caracas, as Manager of the Immunology Lab and as embryologist of Fertility Medical Group at the Centro Médico Docente La Trinidad Clinic (CMDLT), the largest IVF program in Venezuela accredited by the Latin America Network of Assisted Reproduction (REDLARA).

Póo joined a pioneer research group led by Dr. Carlos Simón who is a world-renowned researcher in human reproduction and stem cells in reproductive
medicine fields. She achieved the derivation of several human embryonic stem cells lines and made important contributions to the development of approaches for derivation of human embryonic stem cells from single biopsied blastomere preserving embryo viability, working in Spanish National Stem Cell Bank at Valencia, Spain.

In 2011, comeback to work as embryologist in the Valencia Infertility Institute (IVI) at Valencia, Spain, dedicated exclusively to preimplantation genetic diagnosis program. Póo joined IGENOMIX in end 2012, where she serves as embryology director providing technical support to fertility clinics around the world for the development of PGS-PGD programs and develops theoretical and practical trainings on techniques for improving the results of ART programs.

Also develops educational activities coordinating national and international courses and works as associate professor of University of Valencia participating in several masters on Assisted Human Reproduction organized by IVI University Institute.

Nasser Al Asmar, MSc Laboratory Manager USA

Nasser Al-Asmar received his Bachelor’s degree in Pharmacy, and a Master Degree in Biotechnology of Human Assisted Reproduction at Valencia University (Spain). He is currently doing his Ph.D. in Human Male Genetics in collaboration with Prof. Hassold at Washington State University.

Nasser Al-Asmar has over 5 years of clinical and research laboratory experience, first at IVI-Valencia Clinic (Spain) at the Preimplantation Genetic Diagnostic Laboratory and then at IGENOMIX (Spain) at the Preimplantation Genetic Screening Laboratory. In his research for the Ph.D., Nasser Al-Asmar has been focused in Human male meiosis, with a main biological question: is there a correlation between Synaptic Initiation Centers and Recombination Sites in the Prophase I in human male meiosis? In the clinical setting, he has extensive experience in the study of chromosomal abnormalities in embryos and spermatozoa using array CGH technology and fluorescence “in situ” hybridization.

Pere Mir, MSc Laboratory Manager Delhi, India

Pere Mir Pardo has a Degree in Sciences at the University of Valencia, Spain, and Master's degree in Biotechnology of Human Assisted Reproduction from the same university. He enjoys a rich experience of 7 years in preimplantation genetic analysis (both Preimplantation Genetic Screening for chromosome anomalies and Preimplantation Genetic Diagnosis for single gene disorders). He is currently finalizing his Ph.D., mainly related with the introduction of array CGH technology for clinical practice in Preimplantation Genetic Screening.
Marcia Riboldi, PhD Laboratory Manager Sao Paulo

Marcia Riboldi received his Bachelor’s degree in Biomedicine with Specialization in Clinical Analysis and a PhD Degree in Obstetrics and Gynecology at the University of Valencia (Spain). She has over 8 years of IVF clinic and research laboratory experience.

In Brazil she started in Fertilitat Reproductive Center (Porto Alegre) and Huntington Reproduction Medicine (Sao Paulo) and after continue in Institute Valencian of Infertility – IVI (Spain).

The principal lines of research were: Embryonic and Adult Stem Cells and with queries related to the preservation of the Human Fertility and Gamete Differentiation. Yours doctoral thesis on title: “Isolation, Culture, Characterization and maturation undifferentiated cells in the human testicular biopsies”.

In the clinical setting, she has extensive experience in the study of chromosomal abnormalities in embryos and spermatozoa using array CGH technology and fluorescence “in situ” hybridization then at IGENOMIX (Spain) at the Preimplantation Genetic Screening Laboratory. The current lines of research were endometrial receptivity and embryo implantation.
3. IGENOMIX ADVANCED GENETIC SERVICE PORTFOLIO

Igenomix offers integral genetic services covering all the genetic needs of the IVF unit, from pre-conception phase to pre-implantation to pre-natal.

3.1 PRE-CONCEPTION PHASE

3.1.1 CGT, Genetic Compatibility Test

a) Definition:
This is an important genetic test when planning a family because it helps to determine the risk of conceiving a child with a genetic disease. The test identifies whether the parents carry one or more recessive genetic mutations.

b) Indications:
- **Before attempting a pregnancy by natural means:** For any woman who wants to become pregnant in order to know the risk of transmitting possible diseases to her children.
- **Before an assisted reproduction treatment:** It is advisable to find out the risk of transmission and to be able to determine the best type of treatment in each case.
- **Before treatment with donor sperm or eggs:** In order to be able to select a donor who doesn’t carry the same mutation as the member of the couple who will provide the gametes (eggs or sperm).

3.1.2 ERA, Endometrium Receptivity Arrays

a) Definition:
The ERA is a personalized genetic test to diagnose the state of endometrial receptivity in the window of implantation in women.

This molecular diagnostic tool is used to analyse the expression levels of 238 genes related to the status of endometrial receptivity. Probes for these 238 genes are hybridized with RNA obtained from an endometrial tissue sample in a custom micro array. After hybridization a computerized predictor reads the signal intensities and the samples are classified ‘Receptive’ or ‘Non-Receptive’ according to their specific expression profiles.

The Endometrial Receptivity Array and the computerized predictor (ERA®) was designed, developed, and patented by Igenomix (PCT/ES2009/000386).

The ERA test has shown high sensitivity and specificity in detecting gene expression profiles associated with receptivity. Endometrial stage dating has been classically determined based on histological criteria. However, this method has been shown not to discriminate between fertile and infertile patients and involves a high degree of subjectivity, meaning these results cannot be applied in the clinic. The ERA test overcomes these problems.

To perform this analysis it is necessary to take an endometrial biopsy from women in their natural cycle or hormone replacement therapy cycles, at a time...
corresponding to the phase of endometrial receptivity. That is, in the natural cycle at day 21, seven (7) days after LH surge (LH+7, or 6 days after the follicle rupture, when this is monitored by ultrasound) or after five (5) full days of progesterone impregnation in hormone replacement therapy (HRT) cycles. After the biopsy is taken it is immediately introduced into an 'ERA cryotube' (supplied by Igenomix) which contains a fluid that allows the preservation of the tissue. The biopsy tube is kept for at least four hours in the refrigerator, after which it can be shipped to our facility at room temperature. After its reception, the sample is kept at -80 °C until it is processed.

3.2 **PRE-IMPLANTATION PHASE**

3.2.1 **PGS, Pre-implantation Genetic Screening**

a) Definition:

Pre-implantation genetic screening (PGS) for aneuploidy is a powerful genetic test that may be performed on embryos during IVF treatment to screen for numerical chromosomal abnormalities. PGS is performed on a small embryo biopsy prior to transfer and identifies which embryos are chromosomally normal. Chromosomally normal embryos are the most likely to develop to term and to be born as a healthy baby. PGS testing helps IVF physicians and patients decide which embryos to transfer.

PGS offers comprehensive analysis of all 24 chromosome types: the two sex chromosomes (X and Y) and the 22 other non-sex chromosomes. Normally there are 23 pairs of chromosomes in each human cell. A numerical change in the number of chromosomes is called aneuploidy. Aneuploidy is responsible for the vast majority of spontaneous miscarriages and can result in birth defects and mental retardation in live-born babies. Most types of aneuploidy are not compatible with life. The most common syndromes caused by non-sex chromosome aneuploidies are Down’s Syndrome, Edwards Syndrome, and Patau Syndrome. Aneuploidy is usually not inherited and can involve any chromosome; however, the likelihood of embryos being aneuploid increases with the age of the mother.

Igenomix uses array CGH (comparative genomic hybridization) technology to perform PGS for aneuploidy screening. Our team works with BlueGnome’s 24sure BAC-based arrays. This technology is specially developed for analysis of only a few cells or even a single cell as is required for pre-implantation genetic testing. Validation studies have been performed in our laboratory to optimize DNA quality and amplification. PGS testing with array CGH is 98-99% accurate.

3.2.2 **PGD, Pre-implantation genetic diagnosis.**

a) Definition:

Pre-implantation genetic diagnosis (PGD) for single gene disorders is a powerful genetic test that may be performed during IVF treatment to screen embryos that are at risk of developing a serious genetic disease. PGD is performed on a small embryo biopsy and identifies which embryos are not at increased risk of developing the disease.
PGD for single-gene diseases has two phases:

- **Genetic validation test:** the validation test is performed before the start of the assisted reproduction cycle and requires blood samples from the couple and preferably those of other family members relevant to the case.
  
  We distinguish between
  
  (i) An informative test, i.e. a more general genetic analysis using genomic DNA to check for the more common diseases such as cystic fibrosis, spinal muscular atrophy, Huntington's, etc.

  (ii) A unique PGD genetic analysis protocol using a single cell in cases where less frequent Mendelian inherited diseases are likely to be present.

- **Genetic analysis of embryos:** regarding the embryo analysis, the biological sample obtained from the embryo biopsy is collected in a microtube in a sterile solution; it is then sent in a cold/frozen container to the analysis laboratory. Once received, the sample is maintained at -20°C until the required molecular genetics techniques are performed.

The Igenomix team is made up of the world’s finest experts in the PGD field who are able to design probes for even the most rare and complicated mutations.

Our set-up time needed to develop the probe is the fastest in the country. Igenomix uses state-of-the-art technology for PGD.

Whenever possible, Igenomix uses a multiple detection approach to ensure the most highly-reliable results. Using direct detection, PCR is used to detect the specific disease causing the mutation. Linkage analysis uses PCR to detect informative STR markers that are linked to the disease-causing gene.

Our multiple-detection strategy minimizes the chances of no results or misdiagnosis due to allele drop out (ADO). With our technology, our PGD testing is 98-99% accurate.

**PRE-NATAL PHASE**

### 3.2.3 NACE, Non-invasive Analysis for Chromosomal Examination

**a) Definition:**

NACE is a routine blood test performed in pregnant woman to screen Down’s syndrome and other aneuploidies in the foetus, without putting their pregnancy at risk.

Abnormalities detected by NACE:

**Down’s syndrome (Trisomy 21);** The overall incidence of Trisomy 21 is 1 in 800 births in the general population, but this risk increases with age and reaches to 1 in 35 term births for women 45 years of age.

**Edward’s syndrome (Trisomy 18) and Patau syndrome (Trisomy 13);** The incidence of autosomal abnormalities can be as high as 1 in 160 live births.
Aneuploidies related to sex chromosomes namely, Turner's syndrome (45, X), Klinefelter's syndrome (47, XXY) and XYY syndrome; Sex chromosomal aneuploidies occur in 1 in 500 male births and 1 in 850 female births(1).

3.2.4 POC, Product of Conception using Array CGH

a) Definition:
Genetic analysis of samples collected from pregnancy losses is a necessary tool to identify the etiology of a gestation failure and ensure appropriate advice to the couple undergoing treatment.

Products of Conception (POC) from Igenomix is a test conducted to identify chromosomal abnormalities in pregnancy losses. At Igenomix, these abnormalities are identified with the use of array CGH technology, which allows the study of all 24 chromosomes to detect aneuploidies in fetal tissue.

POC using array CGH has 98.6% accuracy and rules out misdiagnosis as it can detect maternal contamination.

b) Array CGH vs Karyotype:
Reasons to choose POC using array CGH vs Karyotype:

- Cell culture not required with array CGH. At least in 20 % of cases no information is obtained due to cell growth failure with Karyotyping.
- Rules out misdiagnosis as it can detect maternal contamination. With Karyotyping there is a high rate of misdiagnosis, as 30% of cultures contain maternal contamination.
- Higher resolution than conventional karyotype.
- Rapid results in 10-15 working days.