IST-2004-027749
HeC
Health-e-Child

Instrument: Integrated Project

Thematic Priority: IST

D15.2 - Documentation of Training requirements specifications, Training contents standards and Training assessment report of the second course

Due Date of Delivery: 30 June 2008

Actual Submission Date: 14 August 2008

Start date of project: 1 January 2006

Ending: 31 December 2009

Organisation name of lead contractor for this deliverable: **EGF**

Revision […..]

Project co-funded by the European Commission within the FP6 (2002-2006)		
Dissemination level		
PU	Public	X
PP	Restricted to other programmes participants	
RE	Restricted to a group specified by the Consortium	
CO	Confidential	

Document Classification

Title	Documentation of Training requirements specifications, Training contents standards and Training assessment report of the second course
Deliverable	D15.2
Authors	Giuseppe Curcio, Michele Zadra
Work package	15
Version	0.1
Keywords	Training requirements, assessments, cardiogenesis, cardiopathies

Document History

Name	Remark	Version	Date
Giuseppe Curcio	Collection and elaboration of Training material	0.1	20/07/2008
Michele Zadra	Drafting of del. text	0.2	30/07/2008

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1 Executive Abstract

The present Deliverable is part of WP15 Training, within the Health-e-Child Project, leaded by P13 European Genetic Foundation (EGF). The central objective of WP15 is the implementation of state-of-the-art training available to the project participants and the larger community, designed to meet the different individual requirements and training needs.

The second Health-e-Child Training Course in Cardiogenesis and Congenital Cardiopathies was held from June 7st to June 10th 2008 and directed by Professor Giacomo Pongiglione from P03 IGG Istituto G. Gaslini, Genova, and WP9 Leader. The director was appointed and chosen in agreement with the other Health-e-Child Partners in order to guarantee the relevance of the training with the project goals and thematic areas.

The course was intended to provide the clinicians with the basis to understand the developmental models to clinical applications in congenital cardiac diseases.

Besides the *residential Course*, held in the ancient hermitage of Ronzano - 5 km away from Bologna city center - EGF has been offering e-learning services in order to allow the fruition of the HeC courses via the internet.

- Hybrid Courses: this format combines e-learning with traditional learning. During the residential courses, the EGF network of Remote Training Centres (RTCs) connect in Live streaming in order to attend the lectures transmitted during the morning sessions from the Main Training Centre (MTC) at the venue of the School. At the end of the morning a Questions & Answers session is held and the teachers answer in real time from the MTC's venue to the questions collected among the students of the RTCs. During the afternoon session each RTC organizes local workshops.

- On-demand streaming courses: courses and lectures authorized by the speakers are recorded (audio and video), post-processed (editing, graphics etc.) and uploaded on server in order to create multimedia products available on the EGF website for all the users. All HeC Partners will be provided with an username and password and a direct link to the 2nd Course in "Cardiogenesis and Congenital Cardiopathies".

Taking into consideration past experience, on the basis of activities carried out before and during the 2nd Course and considering the related two learning objects produced, the following document presents:

a) the program of the 2nd of the three planned Health-e-Child Courses,
b) abstracts of lectures and workshops (learning object 1),
c) a sample of the didactic material produced by the 2nd Course (learning object 2),
d) a Student's "who's who" and Faculty address book,
e) Student's satisfaction Assessment

The course was attended by 19 students, 12 of them answered a final questionnaire divided in two subcategories for assessing the overall quality of the Course, of the organization and of the lectures and workshops.

The live web casting of the Course has been followed by 1 Remote training centres RTCs and approximately 10 students.

From mid September the Course will be available in the on demand streaming version trough a restricted area of the EGF portal (www.eurogene.org). Each Health-e-Child partner's member will be provide with a password and a user name to access the e-learning service.

2 Program

CARDIOGENESIS and CONGENITAL CARDIOPATHIES:

From Developmental Models to Clinical Applications

Centro Universitario EuroMediterraneo-CUEM

Bologna, Italy – June, 7-10, 2008

DIRECTOR:

G. Pongiglione (Genoa, Italy)

SCIENTIFIC ADVISORY:

R. Ravazzolo (Genoa, Italy)

PROGRAM

Friday, June 6th - Arrival and Welcome Dinner

Saturday, June 7th

Morning Session		
09:00-09:30	G. Pongiglione	General Introduction, Health–e-Child Project
09:30-10:10	A. Postma	Embryology of the Heart (Cardiogenesis)
10:10-10:40	R. Ravazzolo	Gene Signalling Pathways
10:25-10:45		Coffee Break
9:40-10:25	B. Marino	Clinical Introduction to Congenital Heart Diseases
11:30-12:45	A. Rauch	Cardiac Syndromes
12:45		Lunch

Afternoon Session

14:00-14:45	O. Zuffardi	Genomic variation: a continuum from SNPs to chromosome aneuploidy
14:45-15:30	E. Chiappa	Prenatal Diagnosis of Congenital Heart Diseases
15:30-16:00		Coffee Break
16:00-18:00		Concurrent Workhops

Sunday, June 8th

Morning Session

9:00-9:45	A. Postma	Embryology of the Vascular tissue (Vasculogenesis)
9:45-10:30	R. Hennekam	Vascular Malformative Defects
10:30-11:00		Coffee Break
11:00-11:45	P. Dalmonte	Vascular Malformations: Clinical Aspects
11:45-12:30		
12:30		Lunch

Afternoon Session – Tetralogy of Fallot (TOF)

14:00-14:45	G.Pongiglione	Clinical, Radiologic and Echocardiographic Aspects of postoperative TOF (Health-Child Project)
14:45-15:30	M.C. Digilio	Genetic Basis of TOF
15:30-16:00		Coffee Break
16:00-18:00		Concurrent Workshops

Monday, June 9th

Morning Session

9:10-9:55	P. Spirito	Clinical Aspects of Hypertrophic Cardiomyopathies (HCMP)
9:55-10:40	J. Schmitt	Genetic Basis of HCMP: from bench to the clinic
10:40-11:10		Coffee Break
11:10-11:30	O. Milanesi	Clinical Aspects of Atrial Septal Defects (ASD)
11:30-12:15	A. Postma	Genetic Basis of ASD
12:15		Lunch

Afternoon Session – Dilated Cardiomyopathies (DCMP)

14:00-14:45	M. G.Gagliardi	Clinical Aspects of DCMP
14:45-15:30	E. Arbustini	Genetic Basis of DCMP: from bench to the clinic
15:30-16:00		Coffee Break
16:00-18:00		Concurrent Workshops

Tuesday, June 10th

Morning Session

9:00-9:45	M. Tartaglia	Noonan Syndrome
9:45-10:30	A. Baban	Heart Hand Syndromes
10:30-11:00		Coffee Break
11:00-11:45	C. Danesino/ E. Buscarini	Rendu Osler Syndrome in Pediatric Age Group
11:45-12:45		CONCLUSIONS
12:45		Lunch

DEPARTURE

3 Learning object 1: Abstract of lectures

3.1 Saturday, June 7th

3.1.1 Health-e-Child Project – General Introduction (Giacomo Pongiglione)

Health-e-Child represent a new approach for studying a group of congenital heart diseases characterized by right ventricular overload (namely Atrial Septal Defect, Anomalous Pulmonary Venous Return, and Post-operative Tetralogy of Fallot) and the Cardiomyopathies: vertical integration of epidemiologic, clinical, radiologic, laboratory, biologic and genetic data.

The heart diseases that can cause right ventricular overload are many: three of them will be taken in consideration in our study: Atrial Septal Defect, Anomalous Pulmonary Venous Return, and Tetralogy of Fallot post-op. Different genetic causes have been found both for the Atrial Septal Defect and the Anomalous Pulmonary Venous Return whether in isolated or syndromic forms.

Nowadays, new powerful scientific and technologic tools are available to try better understanding of heart diseases with right ventricular overload and cardiomyopathies. These range from potent imagine techniques, such as Three-dimensional Echocardiography, Tissue-Doppler Imaging, Integrated Backscatter, Acoustic Boundary Detection, Color Kinesis and the Magnetic Resonance Imaging that can give a detailed picture of the heart without exposing the child to any harm, to standardized clinical assessment methods and sophisticated genetic techniques.

The aim of this project is to integrate and analyze all the data (epidemiologic, clinical, radiologic, laboratory tests, histologic and genetic) that are collected during the routine care of the child in order to:

- define a classified algorithm for the diagnosis of right ventricular overload. Currently, no standardized form for right ventricular function exists; moreover, this study helps to discover more molecular information to determine genetic causes of disease subgroups, these information in future can guide to more specific and appropriate therapeutic approaches
- produce a classification for the cardiomyopathies in different subgroups according to the identified genetic or non genetic causes, the addition of genetic information will allow a truly personalized structural classification and characterization of the actually disease
- Predict, in each single case, what will be the course of the disease in order to choose the best therapeutic option and the best moment to start conservative treatment or surgical intervention.

This research study has been made possible by a grant of the European Community (Contract no: IST-2004-027749). It represents a huge international effort and involves scientists with different skills (clinicians, geneticist, informatics etc.) in order to arrive for better vision of the child's disease.

Patients affected with Atrial Septal Defect, Anomalous Pulmonary Venous Return, and Tetralogy of Fallot post-op., or cardiomyopathy are enrolled in the study in four of the most important European Paediatric Cardiology Centers (I.R.C.C.S. G Gaslini, Genoa, Italy, Great Ormond Street Children's Hospital, London, UK and Hopital Necker-Enfants Malades, Paris, France, and joined lately by I.R.C.C.S. Bambino Gesù, Rome, Italy).

All epidemiologic, clinical, radiologic, laboratory, biologic, and genetic data will be centralized and analyzed with powerful software techniques by experts in computer science from different European countries.

3.1.2 Embryology of the Heart (Alex Postma)

Congenital heart defects (CHDs) are the most common developmental anomaly and are the leading non-infectious cause of mortality in newborns. A major part of heart formation is the division of a common cardiac atrium and ventricle into right- and left-sided chambers, which represent an essential evolutionary step in the development of the four-chambered heart and is necessary for separation of oxygenated and deoxygenated blood. In humans, failure of atrial or ventricular septation accounts for nearly 50% of CHDs and requires open-heart surgery to restore normal circulation. Although cardiac septal defects are common, the precise molecular mechanisms for cardiac septal closure in humans remain to be elucidated. Some insight in the mechanism has come from mutations identified in the transcription factors CSX (NKX2.5), TBX5 and GATA4. CSX mutations have been identified in individuals with cardiac septal defects with or without conduction abnormalities, individuals with the Holt–Oram syndrome (HOS)—characterized by septal defects, conduction abnormalities and limb anomalies—have point mutations in *TBX5*, and individuals with mutations in GATA4 have non-syndromic forms of cardiac septal defects. Interestingly the GATA4 mutations identified not only diminish the DNA binding affinity of GATA4, but also abrogate physical interaction between GATA4 and TBX5 establishing a direct relation between GATA4 and TBX5. Recently mutations in MYH6, ACTC1 and other new sarcomeric genes have been implicated in atrial septation defects. Recent developments in this areas and new techniques and methods will be discussed.

3.1.3 Gene Signalling Pathways (Roberto Ravazzolo)

Organogenesis proceeds by sequential gene regulatory steps that control cell fates and organization of specialized cell types into complex structures and their related functions. The heart is the first organ to form in the embryo, following gastrulation and establishment of the three embryonic germ layers, being essential to embryonic survival.

Abnormalities in heart development result in congenital heart disease, the most frequent form of birth defects in humans, therefore knowledge of how the heart forms and its molecular and genetic basis is crucial for understanding the genesis of congenital heart disease.

An evolutionarily conserved gene regulatory network functions during heart development. Functional interconnections between myogenic transcription factors, their downstream target genes, and upstream signaling pathways direct cardiac cell fate, myocyte differentiation, and cardiac morphogenesis.

The process of cardiogenesis, requires several different functional pathways, including BMP, FGF, Wnt, Notch.

The Bone Morphogenetic Protein (BMP) pathway, whose member molecules are highly conserved across species will be described in more detail. In general, a BMP soluble ligand interacts with a receptor complex composed by type 1 and type 2 receptors, resulting in phosphorylation of the type 1 receptor and subsequent activation of intracellular signaling pathways. The major signaling pathway is mediated by Smad proteins and gives rise to transcriptional activation of target genes. In this context the example of the *decapentaplegic* (*dpp*) Drosophila protein, and all related proteins acting in the fly system, will be also discussed. The BMP pathway, as well as other important signaling pathways, is highly regulated by several modulator molecules acting at different level from the extracellular, to the cell membrane, and the intracellular compartment. Regulation is an interesting issue for developmental pathways, since the different levels at which regulators exert their effect can be viewed as key steps for functional studies and, possibly, development of future therapeutic intervention.

3.1.4 Cardiac Syndromes (Anita Rauch)

Congenital heart defects (CHD) may be part of many syndromes. The following table provides an overview of mutational frequencies in different CHDs with known molecular defect in which congenital heart defects are a major symptom. (+++ microdeletion)

CHD	Gene	Frequency of mutations	Phenotype	Penetrance
Konotruncal defects				
PA-VSD	TBX1+++	40-50%	DGS/VCFS	reduced
IAA Type B	TBX1+++	50-80%	DGS/VCFS	reduced
TAC	TBX1+++	30%	DGS/VCFS	reduced
Fallot-Tetralogy	TBX1+++	4-21%	DGS/VCFS	reduced
Fallot-Tetralogy	NKX2.5	4%	non-syndromal	low
	FOXC2	~100%	Lymphedema distichiasis syndrome	For CHD 7%
Pulmonal stenosis (valvular)	PTPN11	50-60% 90%	Noonan LEOPARD	Nearly complete
Peripheral pulmonal stenosis, Fallot-Tetralogy	JAG1	60-75%	Alagille syndrome	high
Peripheral pulmonal stenosis	ELN	35%	non-syndromal	incomplete
	ELN+++	96%	Williams-Beuren syndrome	for PPS reduced
Supravalvular aortic stenosis	ELN	35%	non-syndromal	reduced
	ELN+++	96%	Williams-Beuren syndrome	for SVAS reduced
ASD without AV-Block	Cx43	100%	Oculodentodigital Dysplasia	complete

ASD/VSD	TBX5	30-35%	Holt-Oram	high
	SALL4	63% / 4%	Okihiro, Holt-Oram	high
AVSD	EVC	22%	Ellis-van Creveld, Polydaktyly with dental anomalies	AD and AR complete
	EVC2	?	Ellis-van Creveld	AR complete
PDA	TFAP2B	?	non-syndromal, + VSD and other CHD	high
		60%	Char syndrome	complete for PDA reduced

Reference: Rauch A und Hofbeck M: Herzfehlbildungen, in Ganten/Ruckpual (Hrsg.) Molekularmedizinische Grundlagen von fetalen und neonatalen Erkrankungen, Springer-Verlag, Berlin, Heidelberg 2005

3.1.5 Genomic variation: a continuum from SNPs to chromosome aneuploidy (Zuffardi)

On 2003 it had been solemnly announced that the human genome project was ended with the 99% of the genome that had been sequenced at an accuracy of 99.9%. The solemnity of the announcement was due to the fact that, having sequenced the genome of few individuals, the scientists thought to have in their hands the genome of the entire humanity. This was due to the conviction that the genome of healthy individuals was identical by 99.9%, the main differences apparently consisting in changes of single base pair (SNPs) that account for 0.1% of the genome. However, the following year two papers cancelled these certainties by showing that the genomes of healthy individuals may differ in many regions, sized at least 100 kb but even few Mb, that can be duplicated or deleted. These data had been soon confirmed and enlarged leading to the conclusion that about 17% of our genome can be duplicated or deleted in healthy individuals. The analysis of these genome copy number variations (CNVs) demonstrated that some CNVs are in fact without phenotypic effect, others act as factors of susceptibility to complex diseases, others act as dominant mutations and, finally, others cause contiguous gene syndromes similarly to unbalanced chromosome rearrangements. The genome-wide array analysis of some chromosomal abnormalities detected through the conventional cytogenetic showed also unexpected results and more complex than expected imbalances.

3.1.6 Prenatal Diagnosis of Congenital Heart Diseases (Enrico Chiappa)

Prenatal diagnosis of heart disease begins in the early '80s and its development coincides with the extraordinary progress of echocardiography which characterized the decades ahead. The fetal cardiology is now one of core activities in every referral centre and generates specific needs in carrying out programmes of prenatal screening of congenital heart defects, training of the personnel involved and allocation of services. Because of the growing number of cases detected in fetal age and the unavoidable number of terminations of pregnancy, the incidence of congenital heart defects at birth may be so affected as to reduce the workload of cases managed postnatally. On the other hand, given the climate of competition among centres of paediatric cardiology and cardiac surgery in many developed country, in utero transportation after prenatal diagnosis can guide a stream of cases of congenital heart diseases towards the best centres, expanding their geographical area of referral.

Fetal echocardiography is a powerful tool for diagnosis of fetal arrhythmias of all kinds. In case of incessant supraventricular tachycardia, this technique allows to guide the drug treatment which can be lifesaving in the majority of cases.

Prenatal diagnosis not only improves the preoperatory conditions in most patient but also reduces the mortality and morbidity in selected types of heart disease, such as transposition of the great arteries, hypoplastic left heart and aortic coarctation.

Usefulness of transcatheter aortic valvuloplasty performed in the fetus with critical aortic valve stenosis is still controversial. Until the potential benefits are not confirmed in controlled studies, this technique should be considered an experimental procedure. In the coming years, progress are expected in this area by introducing new techniques and materials resulting from dedicated research programmes.

A timely and accurate prenatal diagnosis allows counseling for parents who can be more aware and involved in decisions necessary to manage at the best fetuses with congenital heart disease. These advantages may reduce also the risk of legal litigation for missed fetal ultrasonographic diagnosis.

Since cases of heart disease detected in utero are usually more serious and complex, their management entails higher costs. Therefore, centres with a high number of fetal referrals should receive protected funds, proportionate to their needs.

3.2 Sunday, June 8th

3.2.1 Embryology of Vascular tissue (Alex Postma)

Congenital heart defects (CHDs) are the most common developmental anomaly and are the leading non-infectious cause of mortality in newborns. A major part of heart formation is the division of a common cardiac atrium and ventricle into right- and left-sided chambers, which represent an essential evolutionary step in the development of the four-chambered heart and is necessary for separation of oxygenated and deoxygenated blood. In humans, failure of atrial or ventricular septation accounts for nearly 50% of CHDs and requires open-heart surgery to restore normal circulation. Although cardiac septal defects are common, the precise molecular mechanisms for cardiac septal closure in humans remain to be elucidated. Some insight in the mechanism has come from mutations identified in the transcription factors CSX (NKX2.5), TBX5 and GATA4. CSX mutations have been identified in individuals with cardiac septal defects with or without conduction abnormalities, individuals with the Holt–Oram syndrome (HOS)—characterized by septal defects, conduction abnormalities and limb anomalies—have point mutations in *TBX5*, and individuals with mutations in GATA4 have non-syndromic forms of cardiac septal defects. Interestingly the GATA4 mutations identified not only diminish the DNA binding affinity of GATA4, but also abrogate physical interaction between GATA4 and TBX5 establishing a direct relation between GATA4 and TBX5. Recently mutations in MYH6, ACTC1 and other new sarcomeric genes have been implicated in atrial septation defects. Recent developments in this areas and new techniques and methods will be discussed.

3.2.2 Vascular Malformative Defects (Raul Hennekam)

Clinical and Molecular Genetics Unit, Institute of Child Health, Great Ormond Street Hospital for Children, London, UK and Department of Paediatrics, Academic Medical Centre, Amsterdam, The Netherlands

Vascular malformations are common birth defects, and extremely variable in their presentation. This has hampered adequate definition of the various phenotypes. Indeed each year numerous 'new nomenclatures' for vascular malformations are published.

Here I use the nomenclature as accepted by the International Society for the Study of Vascular Anomalies. As the developmental biological and molecular genetic background will be discussed by others, I will only discuss the clinical aspects of vascular malformation. This will include:

- Vascular tumors
    - hemangioma
    - kaposiform hemangioendothelioma
- Macular stains
- Vascular malformations
    - simple (capillary / venous / lymphatic / arterial)
    - combined
    - syndromic
        - Klippel-Trenaunay syndrome
        - Sturge-Weber syndrome
        - Proteus syndrome
        - Maffucci syndrome
        - Blue rubber bleb syndrome
        - Macrocephaly-cutis marmorata

3.2.3 Vascular Malformations: Clinical Aspects (Piero Dalmonte)

Identification and correct classification of vascular anomalies were historically characterized by the use of confusing nomenclature. In 1982 Mulliken and Glowaki published a classification of vascular birthmarks grouping them into two major categories**:**

(A) Malformations and (B) Vascular Tumors (hemangiomas).

This Mulliken's biologic classification is actually the accepted classification of the International Society for the Study of Vascular Anomalies (ISSVA).

(A) <u>Vascular malformations</u> are always present at birth, grow proportionately with the child and never regress, many of them worsening with puberty or after trauma or infective diseases. They can be further subdivided into groups on the basis of their vascular components (capillary, venous, lymphatic or a combination of each) and flow characteristics (slow-flow and high-flow malformations).

Vascular malformations are also frequently classified by eponyms when they are components of syndromes.

The most frequent clinically recognized vascular malformations are:

a) **Capillary malformations (CMs)**: they include teleangectases and port-wine stains of the skin; present at birth, , they may present as small patches or involve an entire limb or portion of the face or the trunk . They may occur in association with other congenital malformations. They are characterized by a colour of the cutaneous lesion from pink to violet, and response to pulsed dye-laser treatment.

b) **Venous malformations (VMs):** they usually present as a soft, compressible blue masses that enlarge when the affected area is in a dependent position; the blue colour is patognomonic. They may extend into the skeletal muscles and joints. Pain is a common complaint. Other complications of VMs include phelobolith formation and bleeding diathesis. Localized intravascular coagulation within a VM may result in abnormal coagulation profiles.

Magnetic Resonance Imaging (MRI) is helpful in confirming the diagnosis of a VM and delineating the extent of involvement.

A multidisciplinary approach to therapy is essential for management of VMs, because their specific management depends on the location of the lesion. They may be treated with surgical excision, sclerotherapy, or a combination of both. Surgical excision alone may be difficult because of the widespread nature, risk of bleeding, and possibility of recurrences.

c) **Lymphatic malformations (LMs**): they are developmental anomalies of the lymphatic system that result in abnormalities in lymphatic flow. We can distinguish diffuse and localized LMs. Diffuse LMs represent a group of disorders of the skin and subcutaneous tissue that may be primary (congenital) or secondary (acquired) ; a diffuse LM is also known as lymphedema.

Localized congenital LMs are often referred as "lymphangiomas", and can be divide into macrocystic or deep lesions and microcystic or superficial lesions. Usually asymptomatic, localized LMs may be associated with local pain or tenderness. They present as poorly circumscribed subcutaneous masses that expand over time. Neck and axilla are the most common localizations.

Microcystic LMs are frequently located over proximal limbs, upper arms and chest, and commonly present as persistent crops of thin-walled vesicles or hyperkeratotic papules arranged irregularly in groups; the most common symptom is recurrent oozing of clear fluid (lymphorrea). Complications include ulcerations, bleeding, and secondary infection.

LMS are frequently diagnosed clinically.Ultrasonography is an excellent method of differentiating macrocystic from microcystic LMs. Once the diagnosis is established, symptomatic LMs are more commonly managed with surgical excision; multiple procedures my be required and often complete excision may not be possible. Recurrence is a risk for partially excised lesions.

Percutaneous sclerotherapy is a good alternative to surgery.

d) **Arterial malformations (AMs):** they are not vascular malformations included in the Mulliken's biological classification, which mainly focus on superficial vascular tumors and malformations, but for completeness they have been here reported.. Ms are sporadic congenital anomalies which can be subdivided into subgroups: stenotic lesions, aneurysms, vascular slings and vascular rings (double aortic arch) and anomalous origin of great arteries (subclavian and innominate arteries). The specific management (surgery or interventional radiologic procedure) is usually expressed after MR and angiography.

AMs may also occur in association with other congenital malformations (PHACE Syndrome).

e) **Arteriovenous malformations (AVMs**): they are fast-flow vascular lesions composed of dysmorphic arterial and venous vessels connected directly to one another without an intervening capillary bed.. AVM may progress through 4 different stages and can be scored by severity using the 1990 ISSVA-accepted Schobinger clinical staging.

Stage I lesions are in the quiescent phase and are asymptomatic (the AVM is not apparent or has the appearance of a port-wine stain); the presence of increased warmth, a bruit , or thrill suggests a high–flow component. Stage II represents expansion; tortuous draining vessels appear, and the lesions enlarge and darken. During stage II, deep destruction occurs with spontaneous necrosis, chronic ulceration, pain and hemorrage. Finally, stage IV is defined by cardiac decompensation (high-output cardiac failure).

The initial diagnosis is clinical; a Doppler scanner usually confirms the diagnosis; MRI/magnetic resonance angiography allow to define the extent of the lesions. Treatment may be difficult: ultimodal treatment, including preoperative embolization and complete surgical resection, is usually necessary for the management of AVMs.

Vascular malformations are sometimes associated with underlying disease or systemic anomalies, and several **syndromes** are well defined and familiar to most physicians. These syndromes can be categorized on the basis of the characteristics of the associated vascular malformation.

We report here the most common syndromes.

1) Syndromes associated with vascular stains and slow flow:

- **Sturge Weber Sybdrome (SWS**). It is a congenital disorder characterized by a dermal CM of the face (port-wine stain) occurring in association with vascular malformations of the leptomeninges and the eye.; the symptoms include seizures, hemiplegia, mental retardation, and glaucoma. Typical of SWS is the presence of intracranial calcifications. The risk for SWS is determined by the distribution of the port wine stains; SWS occurs exclusively in patients whose vascular malformation is located in the first branch of the trigeminal nerve.
- **Klippel Trenaunay Syndrome (KTS)**: it is characterized by a superficial vascular stain of the skin in association with soft tissue and bone hypertrophy of the affected limb, and varicose veins with or without deep venous anomalies. Lymphatic anomaly of the limb may occur (slow-flow capillary venous complex). One of the more common venous anomalies involves the full length of the lateral limb, and it is thought to represent persistence of the embryonic dorsal vein system that normally disappears in the first trimester. Varicose veins are associated with limb hypertrophy.

A variety of symptoms may be associated with venous anomalies. They include pain, trombophlebitis, cellulites, venous stasis dermatitis and ulcers.

KTS should be suspected in all infants with capillary malformation involving a limb.

2) Syndromes associated with vascular stains and high-flow lesions (AVM):

- **Parke Weber Syndrome:** it is a condition of KTS associated with the presence of significant arteriovenous shunting of the involved limb and severe limb overgrowth (high-flow complex).
-

3) Syndromes associated with VMs, LMs, or mixed malformations:

- **Blue rubber bleb nevus syndrome**: it is a rare sporadic disorder characterized by venous malformations of the skin and gastrointesrinal tract. The most characteristic lesion of the skin is a compressible blue subcutaneous nodule. Gastrointestinal tract venous malformations cause the most significant morbidity in blue rubber bleb nevus syndrome. The entire bowel may be affected.Patients may have only anemia from chronic occult intestinal blood loss and melena. In addition to anemia, comsumptive coagulopathy is commonly observed, with high D-dimer levels. Bleeding, local pain and compression are the typical symptoms.

- **Proteus Syndrome**: it is a rare sporadic disorder characterized by soft tissue and bone hypertrophy with gigantism of the hands and feet, hemi-hypertrophy, exostosis, cranialhyperostosis, visceral hamartomas (including lipomas), vascular anomalies, epidermal nevi and subcutaneous masses. It has such variable clinical characteristics that concern has been expressed for misdiagnosis and over-reporting of this syndrome. Capillary, venous, lymphatic and combined slow-flow malformations identical to KTS may occur. The pathogenesis is poorly understood. The diagnosis is established on the basis of clinical features. Management to date is largely supportive.

- **Maffucci Syndrome**: is a rare sporadic genetic disorders typically comprising enchondromas and vascular anomalies (both nodules of venous malformation and of a distinctive tumor, the spindle cell hemangioendothelioma). Affected people appears normal at birth., and the disease usually manifests in early childhood. enchondromas present as hard nodular lesions, most frequenly in the phalanges and long bones. The spindle cell hemangioma is a vascular tumor presenting as a cutaneous mass commonly found beside the venous nodules. Complications include short stature, bone irregularities, shortened long bones and pathologic fracture.

- **Gorham Stout Syndrome**: (disappearing bone disease, phantom bone disease) is a very rare syndrome characterized by intraosseus and soft tissue vascular malformations and osteolysis. The most common finding seems to be a lymphatic malformation.

4) Other Syndromes associated with cutaneous vascular stains lesions:

- Hereditary hemorrhagic teleangectasia (Rendu Osler Weber S) is an autosomal dominant disorder characterized by mucocutaneous and visceral teleangectases and AVMs. Symptoms: recurrent epystaxis from mucosal teleangectasia, bleeding from gastrointestinal tract teleangectases, pulmonary AVMs responsible of emboli and stroke.

Other neurology findings include cerebral AVMs resulting in migraines and seizures.

The diagnosis is established when 3 of the following feature are present: epistaxis, teleangectases, visceral lesions (AVMs) and a family history. Meeting 2 criteria suggests a possible or suspected case.

(B) <u>Capillary immature (infantile) hemangiomas</u> are the more common benign vascular tumors in infancy (95% of vascular tumors). They appear in the first month of life and are characterized by rapid postnatal proliferation (first 6-8 months of life) and slow spontaneous but unpredictable involution (6-8 years). In the first year of life they can present different complications: ulceration with secondary infection, hemorrage, functional problems.

Facial hemangiomas represent the most troublesome localizations, which frequently require medical and/or surgical treatment in the first years of life

Treatment is based on early medical therapy (steroids, alfa-2-interpheron, chemotherapy), surgery (emergency, early and late surgery) and lasertherapy (pulsed dye-laser)

Indications to early medical therapy are the rapid evolution, extensive facial localizations, functional problems and the presence of visceral hemangiomas (mainly liver and larynx).

Emergency surgical therapy (under the first year of age) is more commonly required for functional ophthalmologic complications in palpebral and peri-orbital hemangiomas, in the case of extensive ulcerations (mainly labial) and in the case of significant bleeding.

Visual impairment, proved or in process, needs to be confirmed with an ophthalmologic evaluation, and includes permanent ambliopia, astigmatism, loss of the binocular vision, strabism and displacement of the eye ball. The feasibility of surgery needs to be demonstrated by a preoperative MRI.

Early surgical therapy (between 1 and 3 years of age) is usually proposed in facial hemangiomas not suitable of favourable spontaneous involution (severe distortion and asymmetry of cheeks, nose, lips, presence of definitive scars, largely exceeding and infiltrated skin), morphologic conditions associated with a high high risk of late invalidating sequelae.

In the majority of cases, a step-by-step surgical program is proposed for facial localizations

3.2.4 Clinical, Radiologic and Echocardiographic Aspects of postoperative TOF (Giacomo Pongiglione)

Different innovative modalities of analysis of right ventricle in post-operative Tetralogy of Fallot (TOF) will be discussed thoroughly. TOF is one of the most frequent congenital heart diseases, it constitutes 25% of all paediatric cardiac surgery operations. To date, around 5% of Tetralogy of Fallot have a known genetic cause.

3.2.5 Genetic Basis of TOF (M. Cristina Digilio)

Tetralogy of Fallot (TOF) accounts for 5.4% of all congenital heart defects and, excluding transposition of he great arteries, represents fro about 60% of conotruncal defects. In one third of patients TOF is a syndromic defect, associated with chromosomal anomalies, monogenic syndromes and genetic associations with extracadiac defects.

Chromosomal anomalies are involved in about 12% of the cases, prevalently trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome). Advances in cytogenetic and molecular techniques have led to the identification of syndromes due to submicroscopic defects, such as the microdeletion of chromosome 22q11.2 (DiGeorge/Velo-Cardio-Dfacial syndrome). Among single gene defects, Alagille syndrome is known to be frequently associated with TOF. This syndrome is due to mutations in the *JAGGED1* gene. Several conditions with multiple malformations have TOF as their cardiac component. These include CHARGE syndrome, VACTERL association, and Goldenhar syndrome (Oculo-Auriculo.-Vertebral spectrum). Specific anatomic characteristics can be detected in congenital heart defects associated with specific syndromes. Patienst with TOF and deletion 22 have frequently additional cardiac defects, including right or cervical aortic arch, hypoplasia or absence of the infundibular septum, absence of the pulmonary valve, and discontinuity and diffuse hypoplasia of the pulmonary arteries. Patient with TOF and Down syndrome have frequently a particularly large ventricular septal defect, and, if a common atrioventricular valve is present, the morphology is that of the Rastelli type C atrioventricular canal defect.

Non-syndromic TOF is often a sporadic occurrence in the families, but multiple affected family members can also occasionally been found. The “multifactorial model of inheritance is probably involved in the majority of the cases, suggesting that several genetic loci can interact together in association with environmental factors. Nevertherless, familial recurrence of TOF within affected members supports monogenic or oligogenic inheritance in selected cases. The number of genes known to be involved in non-syndromic TOF is low. Up-to-now, only mutations in NKX2.5 (4% of TOF cases), JAGGED1 gene, FOG2 gene (4% of the cases) have been found. In practical genetic counselling, the recurrence risk for congenital heart defect among siblings of patients affected by TOF is considered about 3%.

3.3 Monday, June 9th

3.3.1 Clinical Aspects of Hypertrophic Cardiomyopathies

Hypertrophic cardiomyopathy (HCM) is the most common familial genetic disease of the heart (about 1/1000). The disease is caused by mutations in any one of 12 genes encoding proteins of the cardiac sarcomere. The features of HCM include marked and asymmetric left ventricular (LV) hypertrophy, a non-dilated LV cavity and preserved systolic function. The clinical course is extremely heterogeneous. Many patients remain asymptomatic throughout life, others develop severe heart failure, and some die suddenly, often at a young age and in the absence of previous symptoms. However, LV wall thickening resembling HCM may also occur in some children and adults affected by other rare genetic diseases, such as Danon or Anderson-Fabry disease. Therefore, in selected patients, only DNA analysis may have the potential for establishing the correct diagnosis.

3.3.2 Genetic Basis of HCMP:from bench to the clinic (Joachim Schmitt)

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained hypertrophy and histopathologic findings of myocyte fibrosis and myofibrillar disarray. It is the most frequent cause of sudden cardiac death in the population under the age of 35 years and the most common cardiovascular disease that is inherited in an autosomal dominant trait (prevalence of 200 per 100,000 individuals).[1] Intriguingly, the vast majority of genetic defects that cause HCM are located in genes that encode for proteins of the contractile apparatus of the cardiomyocyte. At present, almost 500 different HCM causing gene variants have been identified in 13 genes that are all related to the myocyte contractile units (compare table below).

Table: Genes, in which genetic defects can produce HCM.

Gene	Protein	percentage of all cases
MYH7	β-Myosin heavy chain	44
MYBPC3	Myosin-binding protein C	35
TNNT2	Troponin T	7
TNNI3	Troponin I	5
TPM1	α-Tropomyosin	2.5
MYL2	Regulatory myosin light chain	2
MYL3	Essential myosin light chain	1
ACTC1	Actin	1
TTN	Titin	<1
CSRP3	Muscle LIM protein	<1
TCAP	Telethonin	<1
MYOZ2	Myozenin 2	<1

VCL	Vinculin	<1

The vast majority of HCM causing gene defects are heterozygous point mutations that produce stable proteins. As a result, HCM is not caused by the loss of protein but by the alteration of protein function.[3] The incorporation of mutant protein into the contractile apparatus of the heart has been shown to modify its regular mechanical properties - most prominent were altered actin-myosin interactions resulting in increased myofibrillar tension, prolonged myocardial relaxation, and normal or enhanced contractility.[4,5] Apart from such common characteristics of HCM hearts, there is considerable phenotypic variabilty, e. g. the degree of cardiac hypertrophy, the age of disease onset, the risk of fatal arrhythmia and/or heart failure among HCM patients are distinct. A possible explanation for this variation is the diversity of genes, in which mutations can provoke HCM. In fact, MYH7 mutations generally produce a higher extent of hypertrophy than other HCM genes, MYBPC3 variants often show late-onset hypertrophy and TNNT2 defects are associated with higher incidences of sudden cardiac death.[6] On the other hand, clinical symptoms are often variable among individuals with identical mutations, indicating that genotype alone does not determine the course of disease.[7] Variables that seem to critically influence disease progression are the individual genetic background, modifier genes, lifestyle and gender.[8,9]

The diversity of disease causing mutations and the phenotypic diversity suggest that the underlying molecular mechanisms also may be distinct. However, dysregulation of intracellular calcium may play a central role in the pathogenesis of HCM.[2] In the heart, calcium acts as a central coordinator of excitation-contraction coupling and a key molecule in the activation of hypertrophic signaling pathways. Studies on HCM myocytes demonstrated an increase in calcium sensitivity, which could explain the observation of higher myofibrillar tension, often enhanced ATPase activity and increased energy consumption in HCM hearts.[4,10] Furthermore, beat-to-beat calcium cycling between the sarcoplasmic reticulum (SR), the cytosol and the contractile units of every myocyte seems to be altered in HCM hearts.[11,12] Specifically, SR calcium contents and SR calcium release with every heart beat were shown to be low in mouse myocytes with HCM causing myosin mutations, suggesting that the mutant contractile apparatus may sequester calcium from regular cycling. Expression levels of the calcium-binding SR proteins calsequestrin and junctin, and of the ryanodine receptor calcium channel, were also decreased in these mice. Strikingly, treatment of mice carrying an HCM causing Arg403Gln mutation in cardiac myosin with the L-type calcium channel inhibitor diltiazem prevented the development of hypertrophy and histopathologic changes of HCM, and also restored normal levels of calsequestrin, junctin, and ryanodine receptor.[12]

Although myocyte calcium regulation appears to be a promising target, additional information about the molecular signals triggered by gene mutations is imperative in order to design effective strategies for the treatment of HCM patients.

3.3.3 Genetic Basis of ASD (Alex Postma)

Upon fertilization, the fertilized egg, or *zygote,* starts the so-called cleavage divisions, roughly one cleavage per day during the first four days, when the *morula* stage has been achieved, At stage stage cells can no longer be arranged in a symmetrical fashion and cells facing the environment start to become different from those facing the inner side. Compaction occurs and a blastula form, with a fluid-filled cavity, an *inner cell mass* which will form the embryo proper and an outer layer, or cytotrophoblast. The transcription factor Oct4, characterizing undifferentiated cells, is present in the inner cell mass, but no longer in the cytotrophoblast, which will contribute to the forming placenta. *Parental imprinting* causes that the homologous chromosomes, derived from father or mother exert different effects on the developing embryo. With implantation the *dorso-ventral axis* of the embryo is established, whereas current knowledge on the development of the *cranio-caudal axis* tends to a random process. Just prior to implantation the inner cell mass becomes organized in two epithelia, the *epiblast,* facing the forming *amniotic cavity* and the *hypoblast*, facing the forming *yolk sac*. Subsequent to these events a unique process start, called *gastrulation*, by which the *extra-embryonic mesoderm* takes origin and the first germ cells can be recognized and subsequently, the three germ layers of the embryo develop, *endoderm, mesoderm* and *ectoderm.* The transcription factor Oct4 only is expressed in the forming germ cells. A prominent structure of the gastrulating embryo is the *primitive streak* and the *primitive node* at its “cranial” end, through which the cells of the epiblast migrate to form the germ layers. At this stage the *left-right axis* of the embryo is formed, by movement of extra-cellular fluid to the left, initiated by the cilia on the node. Impairment of this movement, such as in the Karthagener syndrome cause randomization of the situs. Although at this stage, third week of development, the body axes are established, the embryo is still a flat disc. The next important step in embryonic development is the *folding* of the disc, by which the ventral body wall is formed. It is pertinent to appreciate that the periphery of the embryonic disc in fact is the “navel” of the body, and that the disc grows enormously, but not at the peripheral edge, by which the embryo takes shape and forms a ventral body wall, a process that can be called ballooning, but is called in all text books “folding of the embryo”. After folding, early organogenesis starts in the second month of development. We will discuss these early morphogenetic processes, along with the underlying molecular processes of *differentiation, pattern formation, modulation and maturation in the context of heart and vascular development.*

3.3.4 Clinical Aspects of DCMP (Maria Giulia Gagliardi)

Dilated cardiomyopathy (DCM) is a rare disease in the paediatric population. We analysed the epidemiology, clinical features and role of immunotherapy in the treatment of myocarditis. On the basis of experimental evidence, indicating that autoimmunity might play a role in the development of myocarditis, we treated children affected by myocarditis with immunosuppressive therapy, and we present here our series. The future availability of reliable prognostic markers should allow treatment of only those children with myocarditis who do not spontaneously recover. The possibility that DCM with myoucarditis is a distinct pathological entity from the non-inflammatory form of DCM is suggested.

Conclusion: The high long-term survival rate observed in our children with myocarditis is probably due to the effect of short-term immunosuppression. This result is at odds with previously published series of conventionally treated children, whose survival probability at 1 y was approximately 0.60

Key Words: Children, idiopathic dilated cardiomyopathy, immunosuppression, myocarditis.

3.4 Tuesday, June 10th

3.4.1 Noonan Syndrome (Marco Tartaglia)

Noonan syndrome (NS) is a clinically variable disorder defined by short stature, facial dysmorphisms, multiple skeletal defects, and a wide spectrum of congenital heart defects. The distinctive facial features consist of a broad forehead, hypertelorism, down-slanting palpebral fissures, high-arched palate and low-set, and posteriorly rotated ears. Cardiac involvement is present in up to 90% of affected individuals, with pulmonic stenosis (PV), hypertrophic cardiomyopathy (HCM) and atrioventricular septal defects representing the most common lesions.

Additional relatively frequent features of NS are webbed and/or short neck, variable cognitive deficits, cryptorchidism and hematologic anomalies. While precise epidemiological data are not available, the prevalence of NS is estimated at between 1:1,000 and 1:2,500 live births. The disorder is generally transmitted as an autosomal dominant trait, although many cases result from *de novo* mutations.

NS is genetically heterogeneous, and can result from mutations in the *PTPN11*, *SOS1*, *KRAS*, *RAF1* and *MEK1* genes, which encode for transducers participating in the RAS-MAPK signaling pathway. Defects in the *PTPN11* gene, which encodes the non-receptor protein tyrosine phosphatase SHP-2, account for approximately 50% of cases. The more than 60 mutations that have been reported are almost all missense changes, and promote upregulation of protein function. Genotype-phenotype analysis revealed that PV is more prevalent among individuals with a mutated *PTPN11* allele, while HCM is less common. Two additional distinct classes of missense *PTPN11* mutations have been identified as somatic lesions in hematological malignancies and germline defects in LEOPARD syndrome (LS), which is clinically related to NS. While the former are generally more activating compared to the NS-causing mutations, the latter cause loss of catalytic activity of the phosphatase.

Defects in the *KRAS* proto-oncogene account for roughly 2% of NS cases and engender gain of function in RAS signaling through reduced KRAS GTPase activity or increased GDP/GTP dissociation rate. As documented for *PTPN11*, the distributions of affected residues and amino acid substitutions in NS and cancer appear to be largely mutually exclusive. Missense mutations in *SOS1* occur in approximately 10% of affected individuals. SOS1 is a RAS-specific guanine nucleotide exchange factor that catalyzes the release of GDP from RAS, facilitating the conversion of its inactive GDP-bound form to active GTP-bound RAS. NS-causing *SOS1* mutations are activating and affect residues placed in domains that stabilize the catalytically autoinhibited conformation of the protein. *SOS1* and *KRAS* mutations are associated with specific phenotypes, the former including ectodermal abnormalities, normal stature and absence of cognitive deficits, while the latter a more severe condition approaching CFCS and CS, characterized by pronounced growth failure and mental retardation.

Finally, a small percentage of NS results from missense mutations in the *RAF1* and *MEK1* genes. RAF1 is a member of a small family of serine-threonine kinases, which are effectors of RAS that activate the dual specificity kinases MEK1 and MEK2. Activated MEK proteins, in turn, activate the MAPKs, ERK1 and ERK2. RAF1 gene mutations are observed in about 5% of NS cases and affect residues clustered in three regions of the protein with amino acid substitutions within the consensus 14-3-3 recognition sequence around Ser^{259} accounting for 75% of the mutations. Since 14-3-3 binding at residue Ser^{259} stabilizes RAF1's catalytically inactive conformation and impairs its translocation to the plasma membrane, mutations affecting this motif promote increased RAF1 activity. Additional studies are required to fully understand the functional consequences of mutations affecting residues placed within the other two mutational hot spots within the activation segment region of the kinase domain and at the C-terminus. *RAF1* gene mutations also account for approximately 3% of subjects with LS, and possibly a relevant fraction of pediatric cases with isolated hypertrophic cardiomyopathy. Notably, *RAF1* mutations are almost invariably associated with HCM. A single missense *MEK1* mutation has been reported in two unrelated subjects with sporadic NS. *MEK1* gene mutations are estimated to account for less than 2% of affected individuals. No datum on the effect of the predicted amino acid change on MEK1 function and MAPK signaling is currently available.

3.4.2 Heart Hand Syndrome (Anwar Baban)

In liveborn infants, the frequency of congenital heart defects is 5.9 per 1,000, including conotruncal defects (1.2/1,000), ventricular septal defects (1.2/1,000), patent ductus arteriosus (0.80/1,000), atrial septal defects (0.44/1,000), and dextrocardia (0.10/1,000). Limb defects have an incidence of 1 per 1,000 births, most constituting limb deficiencies. After exclusion of known syndromes, heart defects were recognized with limb deficiencies providing a minimal incidence of 1 in 5,000 births for associated heart/limb anomalies.

The most common heart-hand syndrome is the Holt-Oram syndrome (OMIM 142900). Diagnosis is based on skeletal preaxial radial ray abnormalities that may be unilateral and asymmetrical and can vary from subtle, subclinical findings to frank phocomelia. More than 85% of affected individuals also have cardiac malformations that typically include atrial and/or ventricular septal defects and atrioventricular nodal disease. However, carious cardiac defects had been reported in association with Holt Oram syndrome. The rare Heart-Hand syndrome Type II (Tabatznik's syndrome) is characterized by upper-limb abnormalities (hypoplastic deltoids; skeletal anomalies in the humeri, radii, ulnae, and thenar bones; and brachydactyly type D) and congenital cardiac arrhythmias (junctional rhythms and atrial fibrillation). The poorly understood Heart-Hand syndrome Type III (OMIM 140450) is phenotypically similar and is characterized by cardiac conduction disease (intraventricular delays and sick sinus syndrome). Skeletal malformations are limited to the hands and feet (brachydactyly type C). Septal defects have not yet been identified in patients with Heart-Hand syndrome Type III. Clinical similarities also exist between the heart-hand syndromes and a variety of other less complex autosomal dominant "partial phenocopy" conditions, including familial atrial septal defects (ASDs) with conduction disease (OMIM 108900) that occur without limb deformities, and familial limb malformations that occur without cardiac defects.

In this occasion, different clinical and genetic aspects will be discussed regarding these syndromes and others that can be of significant importance to be taken in consideration in the differential diagnosis where heart and limbs are the essential features.

3.4.3 Rendu Osler Syndrome in Paedriatic Age Group (Cesare Danesino/Elisabetta Buscarini)

Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler-Weber Syndrome (ROW) is an autosomal dominant disorder affecting vascular endothelium and leading to mucocutaneous telangiectases and arterovenous malformations (AVMs). Complications of telangiectases are epistaxes and gastrointestinal bleeding, that may be so severe to require transfusions. Epistaxes and telangiectases are the most frequent symptoms (>95% of the patients). AVMs are mostly observed in liver (60%), lungs (18-70%) and brain (6%) and may cause severe life-threatening complications (Lesca et al., 2007). The phenotype is highly variable, even within families, and penetrance is usually complete by the age of 40 years (Plauchu et al. 1989). Diagnosis of HHT requests the presence of at least 3 out 4 diagnostic criteria, as suggested by the HHT International Advisory Board (Shovlin et al., 2000). The four criteria are: epistaxis (spontaneous and recurrent), multiple telangiectases (at sites as nose, lips, mouth, fingers), visceral lesions (pulmonary, hepatic, cerebral AVMs) and a first-degree relative affected with HHT according to these criteria. In patients with only two criteria, diagnosis is “possible”, and if fewer than two criteria are present, HHT is unlikely; children of affected individuals should be considered at risk in view of the age-related penetrance. About 70-80% of HHT patients carry mutations in either of two genes: *ENG* (OMIM #131195) (HHT1: OMIM 187300) or *ACVRL1* (OMIM #601284) (HHT2: OMIM 600376) which code for a TGFβ receptor type III and I respectively. Evidence for a 3rd locus on chromosome 5q31 (HHT3: OMIM%601011) (Cole et al. 2005) and for a 4th locus on chromosome 7p14 (HHT4:

OMIM%610655) (Bayrak-Toydemir et al. 2006a) has also been reported but the genes have not yet been identified. All these HHTs are clinically indistinguishable. Juvenile Polyposis with Hereditary Hemorrhagic Telangiectasia (JPHT, OMIM#175050) is caused by mutations in the *MADH4* gene, coding for SMAD4, involved in signal transduction of the TGFβ superfamily cytokines by mediating transcriptional activation of target genes (Gallione et al., 2004). The JPHT Syndrome shows the coexistence of juvenile polyposis (OMIM 174900) and HHT in a single individual. *MADH4* mutations may also be observed in unselected HHT patients (Gallione et al., 2006). *ENG* (9q34.1) contains 14 exons, and Endoglin (or CD105) is a membrane omodimeric 624 aminoacid glycoprotein; it contains a large extracellular region, a trans-membrane domain and a short intracellular region. It is highly expressed on the endothelial and haemopoietic cells surface, on activated monocytes, trophoblasts, and some types of leukemic cells (Gougos and Letarte, 1990; Arthur al., 2000). Above 300 mutations are known for *ENG*, mostly nonsense and localized in the extracellular region. Haploinsufficiency is the proven mechanism of action. *ACVRL1, Activin A Receptor, Type II-Like Kinase 1* (12q11-q14) has 10 exons, coding for a 503 aminoacid protein. ALK1 contains a small extracellular, a short transmembrane and a large cytoplasmatic (including a GS and a Ser-Thr kinase) domains. David et al. (2007) suggested that BMP9 and BMP10 are the physiological ligands for ALK1. Over 240 mutations are known for *ACVRL1*, localized over all the coding region (more frequently in exons 3,7,8). Most of them are missense, the pathogenetic mechanism proposed is haploinsufficiency, but for some missense mutations a dominant negative effect has been proposed (Gu et al. 2006). Our group has largely contributed to the study of new mutations in both genes (Olivieri et al., 2002; 2007). *ENG* mutations are more frequently found in patients from Northern Europe and the Americas while Mediterranean populations have a majority of *ACVRL1* mutations (Olivieri et al. 2007). Despite the progresses made, it remains poorly understood how these mutations relate to the molecular and cellular pathophysiology and to the clinical abnormalities in patients. HHT genes are expressed throughout the vascular tree and are believed to regulate critical, general aspects of vascular morphogenesis: cell proliferation, adhesion, differentiation, and apoptosis; but the vascular lesions occur in specific sites and show a focal nature and an age-dependent progression, suggesting that, in addition to mutations, other factors are required to initiate lesion development and influence disease progression.

In children, we face the problems related to genetic testing, identification of defined risks for developing specific symptoms, clinical screening (how early, how extensive).

The most severe clinical problem are related to cerebral AVM and a strong collaboration between genetic and clinical expertise is needed to provide the families and patients with comprehensive information.

4 Learning object 1: Abstract of workshops

4.1 Causes of and mechanisms of adaptation to Left and Right Ventricular Overload in the Fetus (Enrico Chiappa)

In experimental models, the fetal myocardium generates less active tension when compared to adult muscle of the same species. On the other hand, the resting tension is higher in the fetal tissue. These age-relates differences can be explained by the higher proportion of non-contractile proteins within the fetal myocytes. Throughout pregnancy, the myocardium undergo a maturational process characterized by a progressive increase in the number of sarcomeres and in the myofilament content, and the development of transverse tubular system. In addition, deep maturational changes are observed in the cellular processes responsible for the homeostasis of calcium in the myocardium. The contractile response of the immature myocardium improves also with the development of the sympathetic innervation and the status of the β-adrenergic receptors. These maturative processes however do not seem to modify the systolic performance of the fetal heart in the normal physiological condition. The biventricular cardiac output, normalized for body weight, varies very little between 18 weeks of gestation and term. In the fetal lamb the dp/dt max is between 1500 and 3000mmHg/sec, with comparable values to those seen in the adult sheep. As to the Frank-Starling's law, experimental models suggested a less efficient response of the fetal myocardium. However, the peculiar characteristics of the fetal circulation, with parallel arrangement of the two arterial circulations, the mixing of the venous returns, the presence of shunts, the high impedance and low flow of the pulmonary circulation, the low impedance and high flow of the placental circulation make difficult, if not impossible, the interpretation of data of these studies.

On the other hand, the characteristics of the immature myocardium seem to deeply affect the diastolic function of the fetal heart. Pulsed Doppler investigation of blood flow through the atrioventricular valves in the fetus shows a ventricular filling pattern significantly different from that seen in postnatal life. In the adult subject, there is a dominant early diastolic wave (E wave), which expresses the greatest contribution of ventricular relaxation to ventricular filling. In the fetus instead, there is a dominant pre-systolic wave (A wave), which testifies the greatest contribution of the atrial contraction to ventricular filling. In the fetus, the E/A ratio is thus less than 1 and this feature characterize both the right and the left ventricular filling. During pregnancy the E/A ratio increases progressively and approaches to unity at term. This is mainly the result of the rise of the peak velocity of the E wave during pregnancy while the A wave do not change substantially. These observations suggest that the maturational changes in diastolic function are the result of a significant improvement of the ventricular relaxation.

The impaired diastolic function further improves after birth, and most of the characteristics of the mature ventricular myocardium take place within a few weeks.

At any age, the cardiac output is influenced by the complex interplay of four determinants: the pre-load, the after-load, the contractility, and the heart rate. Since the fetal myocardium has a limited ability to increase its contractility or adequately adapt to acute pressure or volume overload, an increased heart rate is often the most effective compensatory mechanism. However, a sustained supraventricular tachycardia may cause severe heart failure in the fetus, even with a structurally normal heart, because of the impaired diastolic function and a greater dependence of ventricular filling by the atrial contraction.

Volume overload, pressure overload, primitive diseases of the myocardium or sustained arrhythmias, when sufficiently severe to overcame the adaptive mechanisms, may produce ventricular dysfunction and heart failure. Because of the characteristics of fetal circulation, the heart failure in the fetus does not involve the pulmonary circulation. Whatever its cause, the pathophysiology of the fetal heart failure passes through the common pathway of right ventricular dysfunction and tricuspid insufficiency.

A series of causes producing right and left ventricular overload will be discussed. Some of these with peculiar manifestation, if not exclusive, in prenatal age.

4.2 MRI Evaluation of operated Tetralogy of Fallot (Pierluigi Festa)

Cardiac MRI is extensively used to assess the patients of all ages after repair of Tetralogy of Fallot, but its greatest clinical utility is in older children, adolescents and adults. Quantitative assessment of right and left ventricular dimensions and function is a key element of cardiac MRI evaluation in these patients. The presence and degree of right ventricular dysfunction is an important determinant of clinical status late after repair of Tetralogy of Fallot, and right ventricular dysfunction is also closely correlated with left ventricular dysfunction, likely through ventricular-ventricular interaction. The degree of pulmonary valve regurgitation measured by Phase Velocity-MRI (Fig.1) is closely correlated with the degree of right ventricular dilation. Another factor affecting the right ventricular function is the presence and extent of an aneurysm in the right ventricular outflow tract (Fig.2-3).

Another technique increasingly used in these patients is post-Gadolinium myocardial delayed enhancement for assessment of myocardial fibrosis (Fig.4). The clinical significance of positive myocardial delayed enhancement in patients after repair of Tetralogy of Fallot still requires further studies.

The goals of the cardiac MRI examination, therefore, include: quantitative assessment of left and right ventricular volumes, mass, stroke volumes, and ejection fraction; imaging of the morphology of the right ventricular outflow tract, pulmonary arteries, aorta, and aorto-pulmonary collaterals; quantification of pulmonary valve regurgitation, tricuspid regurgitation, pulmonary-to-systemic flow ratio (QP/QS) if there is a residual intra-cardiac shunt, and finally distribution of the pulmonary blood flow.

In patients after surgery for Tetralogy of Fallot the following cardiac MRI protocol is used:

3-plane localizing images;

2-Dimensional axial Time of Flight (see the appendix of the introduction chapter);

ECG-gated cine Steady State Free Precession sequences in 2-chamber, 4-chamber planes, and ventricular short axis for the quantitative assessment of both ventricular dimensions, function and stroke volume as illustrated in the appendix of the introduction chapter;

ECG-gated cine Steady State Free Processing sequence on both frontal and sagittal view to evaluate the right ventricular outflow tract;

ECG-gated cine Steady State Free Processing sequence along the long axis of both pulmonary arteries;

ECG-gated cine Steady State Free Processing sequence double oblique 3-chambers for the evaluation of the left ventricle outflow tract and aortic root;

Gadolinium-enhanced 3-Dimensional MRI mainly for the right ventricular outflow tract and pulmonary arteries anatomy (Figg. 2.C and 5), as well as for the assessment of any aorto-pulmonary collateral artery;

ECG-gated PV-MRI sequences perpendicular to the main pulmonary artery (with or without the branch pulmonary arteries), ascending aorta, and atrio-ventricular valves in order to assess the flow patterns;

Post-Gadolinium delayed myocardial enhancement may be used to evaluate the presence of scar tissue. (Fig 4)

The timing of re-operation for reconstruction of right ventricular outflow tract in patients with previous repair of Tetralogy of Fallot is still a matter of debate: ideally the indication should be not too late because of the risk of irreversible right ventricular dysfunction and fatal arrhythmias, not too early because of the limited durability of any biological device used for right ventricular outflow tract reconstruction, particularly in young children.

Only recently, thanks to the use of cardiac MRI in such subset of patients, some cut-off points related to the indexed right ventricular volumes and ejection fraction are emerging for the indication to implant a pulmonary valve in the right ventricular outflow tract. However the end-points of these cut-offs are generally based on the complete post-operative recover of the right ventricular size to the normal value; this could not be a suitable goal, as by dealing with patients who underwent repair of Tetralogy of Fallot, and therefore with patients who had a patch closure of the ventricular septal defect and often an abnormal morphology of the pulmonary vascular tree. Moreover many other variables should be taken into consideration, such as right ventricular outflow tract with trans-annular patch extension with or without aneurism, tricuspid valve regurgitation, elevated right ventricular systolic and/or diastolic pressure, and left ventricular function as well their evolution over time and other clinical and electrophysiological variables.

Therefore due to the accuracy of parameters and information obtained by cardiac MRI, some of them not available by any other diagnostic investigation, nowadays it should be inconceivable any decision-making on patients operated on of repair of Tetralogy of Fallot without a previous targeted cardiac MRI investigation.

4.3 Generation and investigation of mouse models for congenital cardiopathies (J. P. Schmitt)

Over the past two decades, genetic linkage analyses of human kindreds have revealed hundreds of different gene mutations causing congenital cardiopathies (reviewed in 1). However, for designing successful therapeutic strategies the sole identification of the underlying mutations is not enough and a better understanding of the physiological and molecular consequences of these genetic defects is imperative. The remarkable progress in genetic engineering offered the opportunity to introduce specific genetic defects into the mouse genome and, thus, to generate mammalian model organisms of specific human disorders (reviewed in 2). Nowadays, genetically manipulated mice have become indispensable tools in studying the pathogenesis of congenital disease.

There are mainly two approaches to insert specific gene defects into the mouse genome, gene targeting and transgenesis. While gene targeting results in a specific modification of a defined locus in the endogenous genome, transgenesis inserts a genetic construct, which is controlled by its own promoter, at a random genomic site. Strengths and weaknesses of either method are summarized in the table below.

	Transgenesis	gene targeting
strength	- fast - organ / tissue specific expression - for inducible systems: transgene expression can be turned on and off	- modified gene under control of endogenous promoter - precise copy of the human genotype - allows to study recessive alteration - for conditional gene targeting: induction and cell-type specific expression of gene modification possible
weakness	- uncontrolled insertion site - uncontrolled copy umber	- slow - labor-intensive - expensive

The extensive use of genetically modified mice has led to an impressive extension of methodologies to explore mouse physiology - in particular the cardiovascular system (reviewed in 3). Apart from “classical” phenotyping of the mouse heart, such as comparison of heart to body weight ratios or histological examination, this workshop will emphasize on more recently developed techniques that have become standard tools to characterize cardiac morphology and function *in vivo*.

In general, the main difficulties to overcome in adapting existing methodologies for the use in mice were the small size (an adult mouse weighs about 30g) and the high heart rate (500 to 600 beats per minute) of theses animals. High-fidelity microtip transducers have been reduced in size to 1.4 French (≈0.5mm) – small enough to canulate the carotid artery and to advance the catheter into the left ventricular cavity of an anesthetized mouse for continuous recording of left ventricular pressure loops. Special software was designed to analyze the data for critical parameters of cardiac function, such as maximum and minimum left ventricular pressures, speed of left ventricular pressure rise and pressure decay as well as heart rate.

An alternative instrument to investigate the contractile function of a mouse heart at the whole animal level is ultrasound (echocardiography), a technique that also allows the accurate assessment of cardiac morphology in vivo. With the development of high frequency scan heads (around 30Mhz) it became possible to visualize structures as small as a mouse heart (100-150mg) at spatial resolutions of less than 0,1mm. As a logical consequence, measurements of left ventricular wall thicknesses and dimensions by echocardiography have become indispensable for in vivo evaluation of hypertrophic and dilated phenotypes of the mouse heart. Assessment of left ventricular diameters further allows the calculation of fractional shortening, an indicator of cardiac contractile properties. In addition, cardiac contractile function can be estimated using Doppler echocardiography. This method determines blood flow velocities and is useful, e. g. for investigating mitral valve inflow patterns (to evaluate diastolic function) or peak flow velocities in the descending aorta. The latter permits the assessment of pressure gradients after surgical banding of the transverse aorta - a widespread technique to study the left ventricular response to chronic pressure overload.

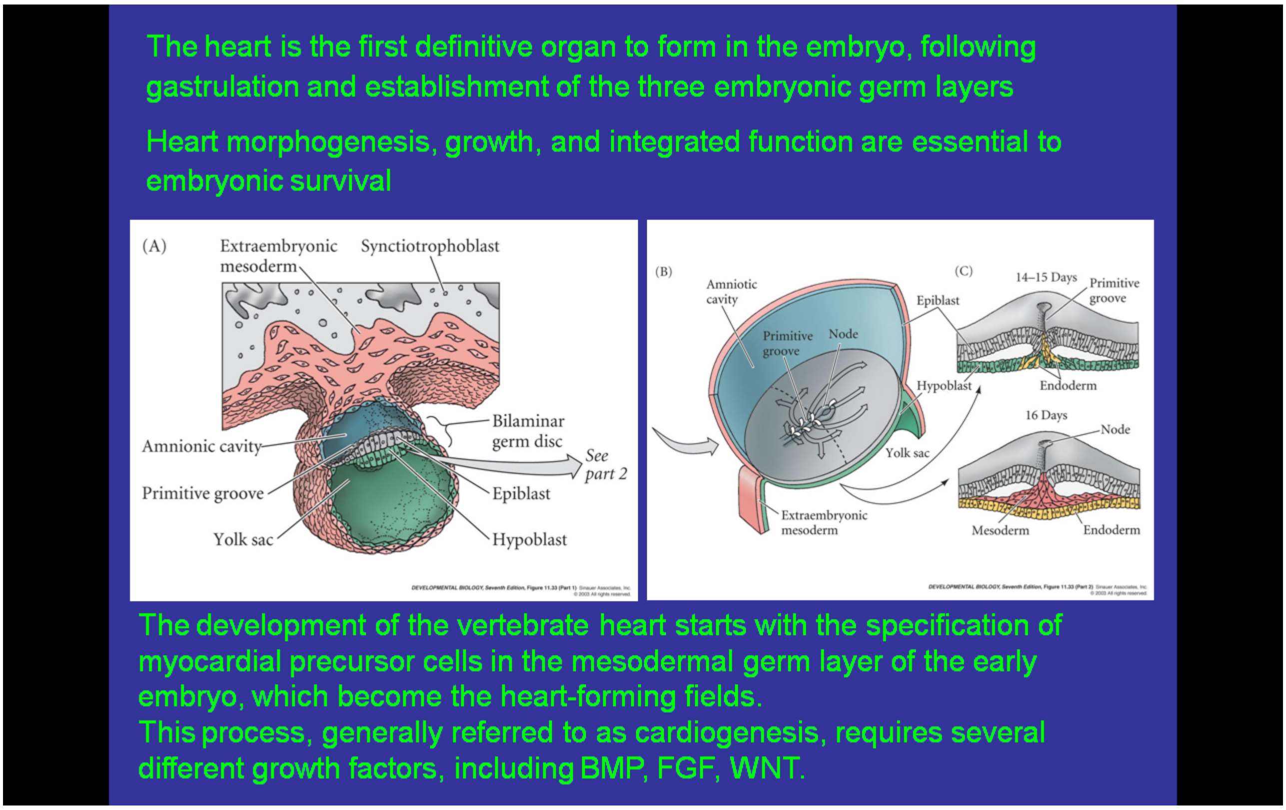
The miniaturization of implantable telemetric transmitters made it possible to continuously monitor physiological parameters in conscious mice, in particular blood pressure, electrocardiogram, body temperature and locomotion activity (reviewed in 4). The holter monitors are small enough for either subcutaneous or intraperitoneal implantation. After surgery, animals are freely moving in their cage, which is positioned on a receiver plate that collects the data into a connected computer for storage and analysis by specialized software. Investigators are using this method (i) for long term recordings, (ii) if normal circadian rhythm is critical in the experimental setting or (iii) to exclude depression of the cardiovascular system by anesthetics.

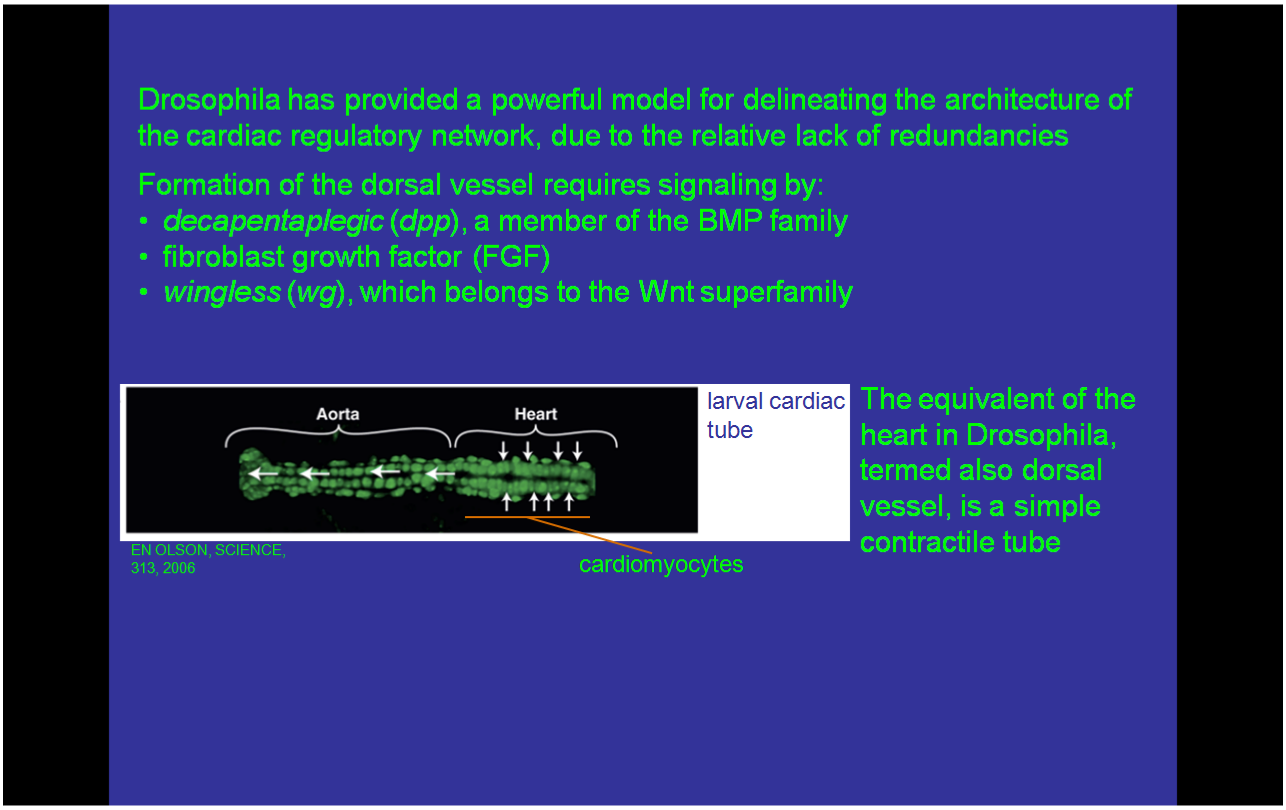
These and other techniques have given rise to a remarkable arsenal of methods that allow cardiovascular phenotyping of genetically engineered mice in order to study the function of various proteins and the consequences of disease causing mutations in living mammalian organisms.

5 Learning object 2: Power Point slides

Power Point slides showed during lectures represent the main didactic tool produced by the second Health-e-Child Course in **Cardiogenesis and Cardiopathies**. In accordance with the aims of the project and in order to enhance the Course content knowledge among the Consortium, the Training Activities partner coordinator EGF has decided to make this didactic tool **the second learning object** arising from the Course. Lecture's slides, which diffusion has been allowed by authors, have been published in a apposite FTP website. Then, each project partner has been provided with password and username to accede site content.

Here below a couple of samples of the didactic material at disposal for Health-e-Child partners, taken from Dr. Ravazzolo's lecture "Gene Signalling Pathways" held the 7th of June during the morning session:




Drosophila has provided a powerful model for delineating the architecture of the cardiac regulatory network, due to the relative lack of redundancies
Formation of the dorsal vessel requires signaling by:
• decapentaplegic (dpp), a member of the BMP family
• fibroblast growth factor (FGF)
• wingless (wg), which belongs to the Wnt superfamily
Aorta
Heart
larval cardiac tube
The equivalent of the heart in Drosophila, termed also dorsal vessel, is a simple contractile tube
EN OLSON, SCIENCE, 313, 2006
cardiomyocytes

6 Student's "Who is Who"

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8 Evaluation

The course was attended by 17 students: 19 of them answered a final questionnaire divided into 2 sub categories for assessing the quality of the lectures and the overall quality of the Course and of the organisation.

8.1 General Satisfaction

The evaluation ranking scale was: 1) excellent; 2) good: 3) adequate; 4) poor; 5) unsatisfactory.

The overall judgement on the course/organization was **good**.

The students particularly appreciated the organization of the programme, the general quality of the lectures and the discussion after the session as well as the chance to present some clinical cases.

Here are some comments collected in the evaluation questionnaires and expressed by the participants together with some proposals about how to improve the quality of some aspects.

On the whole the general quality of the workshops was not so appreciated, even though the average of the evaluations indicates that was almost good. The same score was reached for the qualityof the facilities in the venue and the expectations fulfilled.

Here are some comments written by the students that confirm how some expectations have been disappointed:

- A little more clinical than hoped for
- Final program was ready late
- Some lecturers were too flat during their presentations
- Very variable (regarding the quality of the lectures)
- Workshops about NRI: too much clinical and too long
- Workshop about mouse models: interesting but too detailed
- Workshop RV overload in fetuses: interesting and good
- The topics of some workshops were too clinical, no relevant for a Cardiogenesis course
- Good except from MRI of operated TOF
- It would have been nice to give more time for more detailed presentations of cardiogenesis
- A little more about genetics and less clinic would be appreciated
- No much weight on Cardiogenesis as expected

- I expected more on genetics and embriologic development. So more on gene pathways and their roles in diseases of the heart

- I expected more genetics talks and more recent research work

- It could be nice to have 1 day longer and leave in time to visit Bologna a little more

- EGF staff and faculty were warm and welcoming

- Good location, not too comfortable beds. Fruit for breakfast would be nice

- Very beautiful location in Ronzano. Uncomfortable beds

- Single bedrooms would be better than double

- I would have preferred a single room. The monastery is beautiful.

- Location is a bit isolated. Food is well presented but the variety is very poor. Staff very friendly and helpful

- Too much light in lecture halls

- Bad acustics in the lecture hall

Further suggestions:

- Give more about cardiogenenesis. Idem for epigenetic topics. A fetal pathology component could be helpful. Idem for description of morphology (Andrew Cook and Robert H. Anderson ideal for this)

- A common dinner on last evening would be appreciated. A guided tour in Bologna would be suggested.

- If the course is mainly for geneticists, not cardiologists: more genetics and embriology, the role of the gene in the cardiac problems. Give less about therapies and treatments of cardiac problems.

- Nice to have more on the normal heart and the genes playing a role. Give less clinical lectures (e.g. the NRI lecture)

- Nice to have more on the normal heart and the genes playing a role and pathways

- More about surgery of cardiac malformations

- To have more genetic content, more embriology (molecular embriology included). Aneurysms, Luto, other valve problems are not included. Give less therapy approaches

- Give more genetic talks. The talks of Milanesi and Postma were perfect

- To improve meals, food offer/variation. To include/remove some topics

SUMMARY RESULTS	
Organization of the programme	More than good
General quality of the lectures	More than good
General quality of the workshops	Almost good
Discussion after session	More than good
Expectations fulfilled	Almost good
Location and accommodation	Good
Quality of facilities	Almost good
Overall evaluation	Good

8.2 Lectures

The following table reports the ratings given by students to the 3 indicators. Content relevance indicates the consistency of the contents of the lectures with respect to the topic and their perceived degree of relevance in terms of new knowledge. Form Relevance describes the degree of satisfaction of the students with respect to the way the lectures were organised. Overall Rating indicates the general satisfaction of students. The parameter used for the first 2 indicators are 1-Deficient; 2-Sufficient; 3 Eye-opener. For the third indicator (overall rating) where a 1 to 10 scale was used to express the rating from lowest (1) to best (10).

There is a high appreciation of the lectures expressed by the averages aggregated by indicator: good content relevance (2,34); good form Relevance (2,34) and good overall rating (7,86).

Among the most appreciated lectures we just indicate the ones approaching more to the "eye-opener" level: Genetic Basis of ASD (Postma), Genetic Basis of DCMP: from bench to the clinic (Arbustini), Noonan Syndrome (Tartaglia).

The overall rating shows that the best lecturers were Rauch, Zuffardi, Postma and Tartaglia.

In particular some students suggested in the "Comments" section a closer focus on Cardiogenesis and a lesser clinical approach.

Comments will be used to improve the assessment questionnaires in general and to improve this course in its next editions.

Speaker and Title	Indicators	Averages	Speaker and Title	Question	Averages
Postma – Embriology of the heart	Content Relevance	2,5	Spirito- Clinical Aspects of Hypertrophic Cardiomyopathies (HCMP)	Content Relevance	2,5
	Form Relevance	2,5		Form Relevance	2,3
	Overall Rating	8,45		Overall Rating	7,56
Marino- Clinical Introduction to Congenital Heart Diseases	Content Relevance	2	Schmitt- Genetic Basis of HCMP: from bench to the clinic	Content Relevance	2,6
	Form Relevance	2		Form Relevance	2,4
	Overall Rating	7,67		Overall Rating	7,89
Rauch-Cardiac Syndromes	Content Relevance	2,56	Milanesi- Clinical Aspects of Atrial Septal Defects (ASD)	Content Relevance	2,3
	Form Relevance	2,56		Form Relevance	2,3
	Overall Rating	8,39		Overall Rating	7,78
Zuffardi- Genomic variation: a continuum from SNPs to chromosome aneuploidy	Content Relevance	2,44	Postma- Genetic Basis of ASD	Content Relevance	2,6
	Form Relevance	2,60		Form Relevance	2,6
	Overall Rating	8,50		Overall Rating	8,22
Chiappa- Prenatal Diagnosis of Congenital Heart Diseases	Content Relevance	2,20	Gagliardi- Clinical Aspects of DCMP	Content Relevance	2,1
	Form Relevance	2,20		Form Relevance	2,2
	Overall Rating	7,65		Overall Rating	7,11
Postma- Embryology of the Vascular tissue (Vasculogenesis)	Content Relevance	2,40	Arbustini- Genetic Basis of DCMP: from bench to the clinic	Content Relevance	2,8
	Form Relevance	2,40		Form Relevance	2,8
	Overall Rating	8,25		Overall Rating	9
Hennekam- Vascular Malformative Defects	Content Relevance	2,50	Tartaglia- Noonan Syndrome	Content Relevance	2,6
	Form Relevance	2,50		Form Relevance	2,7
	Overall Rating	9		Overall Rating	8,33

Dalmonte- Vascular Malformations: Clinical Aspects	Content Relevance	2	Baban- Heart Hand Syndromes	Content Relevance	2,5
	Form Relevance	2,20		Form Relevance	2,38
	Overall Rating	7,06		Overall Rating	7,14
Ravazzolo-Gene Signalling Pathways	Content Relevance	2,22	C. Danesino - Rendu Osler Syndrome in Pediatric Age Group	Content Relevance	2,13
	Form Relevance	2,11		Form Relevance	2,13
	Overall Rating	7,38		Overall Rating	7,14
Pongiglione- Clinical, Radiologic and Echocardiographic Aspects of postoperative TOF (Health-Child Project)	Content Relevance	1,6		Content Relevance	
	Form Relevance	1,9		Form Relevance	
	Overall Rating	6,67		Overall Rating	
Digilio- Genetic Basis of TOF	Content Relevance	2,2	TOTAL	Content Relevance	2,34
	Form Relevance	2,1		Form Relevance	2,34
	Overall Rating	7,39		Overall Rating	7,86