Clinical genetic care in diseases predisposing to sudden cardiac death

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Chapter 1

Introduction and outline of thesis

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Introduction

In the past, there has been little collaboration between clinical geneticists and cardiologists, although both parties concern themselves with congenital heart defects and with connective tissue diseases such as Marfan's syndrome. In the nineties of the past century, however, several genes in the field of cardiology were discovered. Among them are the genes predisposing, if mutated, to autosomal dominant diseases with severe consequences like sudden cardiac death, often at young age, cardiomyopathies and primary arrhythmic diseases. Diagnostic DNA-studies have gradually become within clinical reach in index patients as well as in relatives, with our country being one of the forerunners in their application.

It is here that clinical geneticists more often became involved, in patient care as well as in the research setting. In 1996 the first Dutch outpatient cardiogenetics clinics started, located in the academic centres of Amsterdam and Utrecht. Cardiologists, clinical geneticists, genetic counsellors ('genetisch consulenten') and psychosocial workers joined forces to take care of patients with cardiogenetic disease. In these clinics cardiologists mainly perform the cardiologic phenotyping and counselling, while clinical geneticists take care for the dysmorphologic phenotyping in syndromic cases and, together with their co-workers are responsible for the genetic counselling and the organisation and implementation of family studies. After the process of phenotyping and genetic counselling and testing, the patient and his or her risk-carrying relatives are usually sent back or referred to a cardiologist in their neighbourhood.

In contrast with most other genetic disorders, the majority of cardiogenetic diseases are amendable for treatment, that is prevention of progression and particularly of sudden cardiac death, with lifestyle measurements and the use of medication or devices. One of the main goals of counselling and testing in cardiogenetic disorders therefore is to protect as many mutation carriers as possible for the potentially life-threatening consequences of cardiac arrhythmic events. The parallel with genetic counselling in oncogenetics (booming since 1995) is obvious.

Parallel to the opportunities for genotyping, patient numbers in cardiogenetic counselling increased considerably in the past years (Figures 1 and 2).

At the time of this writing all Dutch academic centres have established such clinics, and cardiologists get used to referring eligible patients. Cardiologists, clinical and molecular geneticists, genetic counsellors and psychosocial workers involved in cardiogenetics are joined in the national working group on heritable heart disease of the Dutch Interuniversitary Cardiologic Institute (ICIN) which meets twice a year.

National guidelines for genetic counselling and testing in the abovementioned diseases are still lacking, in the Netherlands as well as in other developed countries, including the USA. Also the assignment of tasks and professional responsibilities in genetic counselling and testing in cardiogenetic diseases clearly have not taken their final shape yet. This is not surprising in the view of the rapid changes in knowledge, care and patient flow.

Figure 1: Numbers of new counsellees attending the AMC cardiogenetic outpatient clinic from 1996

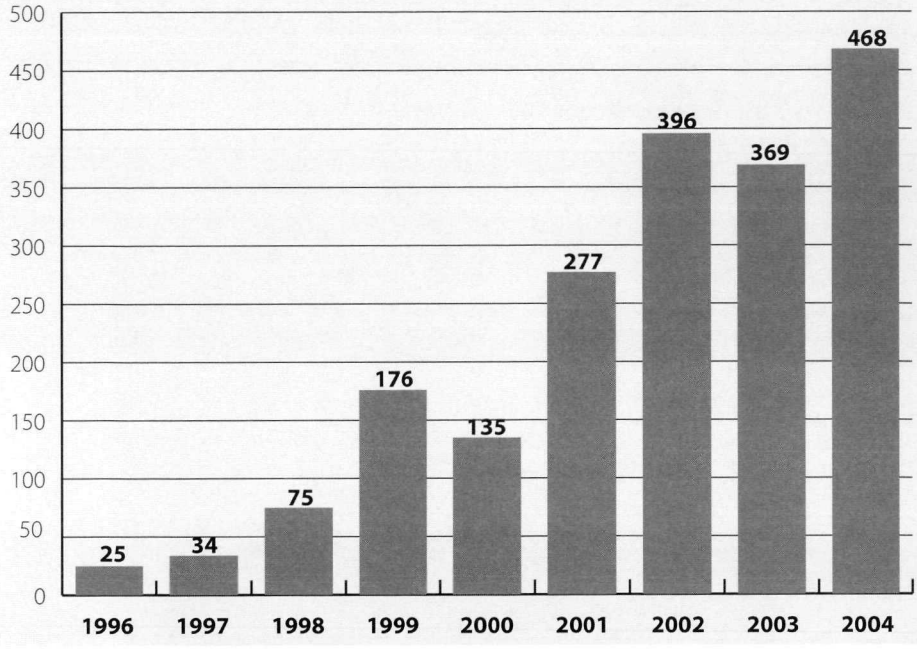
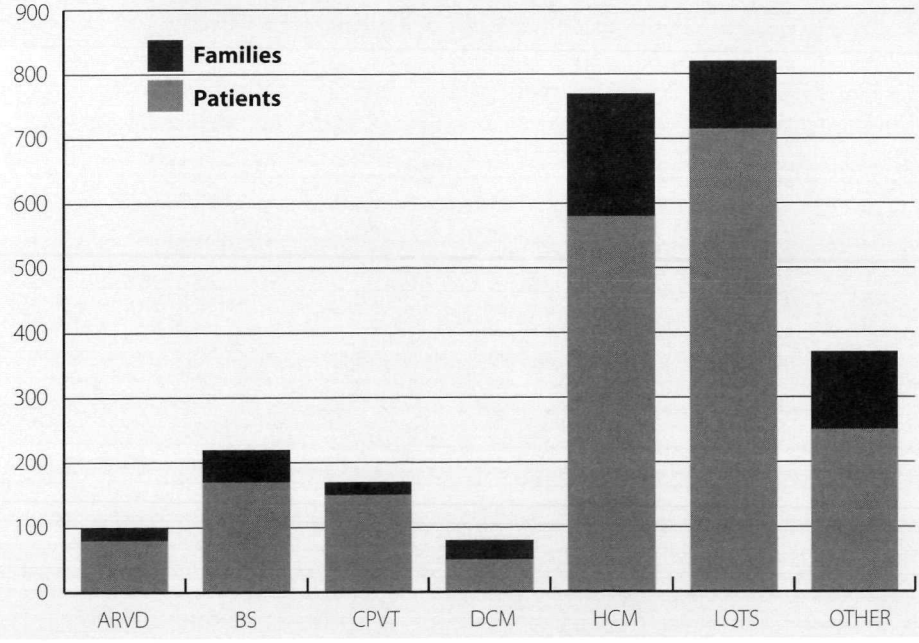


Figure 2: Diseases for which index patients and/or their families attended the AMC cardiogenetic outpatient clinic from 1996-2004



A. Diseases for which families currently attend the cardiogenetics outpatient clinic (table 1)

Primary arrhythmias

1. The Long QT Syndrome (LQTS)

The autosomal dominantly inherited LQTS was independently described by Romano and Ward in 1963 and 1964 respectively [1,2]. In 1957 Jervell and Lange-Nielsen described a very rare form of the same disorder, associated with congenital deafness and inherited in an autosomal recessive manner [3]. The disease is characterised by a prolongation of the corrected QT-interval on the ECG, caused by abnormal lengthening of the repolarization phase of the (ventricular) cardiac action potential, leading to ventricular tachycardia or fibrillation, in particular to 'Torsades de Pointes'. Clinical criteria for diagnosis of LQTS were proposed by Schwartz in 1993 (Table 2) [4]. These criteria were based on the clinical data from that time and have not been refined based on additional molecular genetic data. The structure of the heart by pathological examination is completely normal, as in the other primary electrical diseases. Other organs are not involved, except in cases of the Jervell and Lange Nielsen syndrome and in the very rare syndromic forms of LQTS.

Three prevalent, non-syndromic, forms of the disease are recognised (LQTS types 1, 2 and 3), caused by mutations in the KCNQ1, KCNH2 and SCN5A genes respectively. The first two genes encode for components of separate potassium channels in the cardiomyocyte, the last one for the cardiac sodium channel. Types 4 to 8 are rare. Type 4 is associated with bradycardia and types 5 and 6 are in part associated with drug-induced forms of the LQTS (triggered by the use of certain QT-interval prolonging substances) [5]. Types 7 and 8 are associated with syndromes with a prolonged QT-interval as one of the criteria [6,7].

In the Netherlands genotyping currently identifies the causative mutation in up to 75% of cases. KCNQ1 mutations account for approximately 42-45% of genotyped cases, KCNH2 mutations for another 40-45% and SCN5A mutations for 8-10%. In rare cases compound heterozygous mutations (in the same or in different genes) or mutations in the LQTS4-8 genes are identified. In other western countries LQTS1 seems to occur most frequently [8].

Symptoms of LQTS, if present, consist of palpitations, dizziness, fainting, seizure-like fits and sudden death. They often occur in response to specific triggers including emotions, physical exertion, noise, swimming or (in LQTS3 in particular) during sleep or rest. Manifest disease develops at all ages, starting from birth (sudden infant death syndrome) to middle age. Expression in and between families varies considerably. Because sudden death can be the first symptom of disease, recognition of asymptomatic risk-carriers is of critical importance, given treatment options. Up to 25% of mutation carriers are asymptomatic and have normal QT-intervals (non penetrance) [9]. Untreated symptomatic patients have a mortality of 5% per year. Mortality rates in asymptomatic carriers are unknown yet, but are likely to increase with the individual degree of QT-interval lengthening.

Table 1. Cardiogenetic diseases and their characteristics

Disease	Subtype	Gene	Alias	Chromosomal locus	Inheritance[A]	MIM[B] or Ref[C]	Est.phenotypic prevalence in the Netherlands[D]	DNA-test[E]	Yield of DNA-testing[F]	Additional cardiac phenotype[G]	Additional non-cardiac phenotype[H]	First line prophylaxis in carriersI
Arrhythmia Syndromes												
Long QT Syndrome	LQTS1	KCNQ1	KVLQT1	11p15.5	AD	192500	LQTS: 1:5000	M/L	a)89% b)27%			BB, RL
	LQTS2	KCNH2	HERG	7q35.q36	AD	152427		M/L				BB, RL
	LQTS3	SNC5A	Nav1.5	3p21	AD	603830		M/L				ICD?, RL
	LQTS4	ANK2	ankyrin 2	4q25-q27	AD	600919		L		CD		U
	LQTS5	KCNE1	ISK, minK	21q22.1-q22.2	AD	176261		M/L				BB, RL
	LQTS6	KCNE2	MiRP1	21q22.1	AD	603796		M/L				BB, RL
	LQTS7	KCNJ2	Kir2.1, IRK1	17q23.1-q24.2	AD	170390		M/L			#	NN?, ICD^
	LQTS8	CACNA1C	Cav1.2	12p13.3	DN	601005		M		CHD, CD	syndactyly	BB, RL, ICD?
	JLNS1	KCNQ1	KVLQT1	11p15.5	AR	220400	JLNS: <1:200,000	M/L			congenital deafness	BB,RL, ICD*
	JLNS2	KCNE1	ISK, minK	21q22.1-q22.2	AR	220400		M/L			congenital deafness	BB,RL, ICD*
Short QT Syndrome	SQTS1	KCNH2	HERG	7q35.q36	AD	1	SQTS: ?	M/L				Q?, ICD
	SQTS2	KCNQ1	KVLQT1	11p15.5	AD	2		M/L				ICD
	SQTS3	KCNJ2	Kir2.1, IRK1	17q23.1-q24.2	AD	3		M/L				ICD
Brugada Syndrome	BS1	SCN5A	Nav1.5	3p21	AD	601144	BS: 1:1000	M/L	a)38% b)28%			ICD, Q?
	BS2	?	?	3p22-p25	AD	4		L				ICD
Catecholaminergic Polymorphic	CPVT1	RYR2	?	1q42.1-q43	AD	604772	CPVT: ?	M/L	a)86% b)8%			BB
Ventricular Tachycardia	CPVT2	CASQ2	calsequestrin 2	1p13.3-p11	AR	604772		M/L				BB
Sick Sinus Syndrome	SSS1	SCN5A	Nav1.5	3p21	AR	608567	SSS: ?	M/L				PM*
	SSS2	HCN4	If	15q24-q25	?	605206		L				PM*
	SSS	?	?	?	AD	163800		I		AF		PM*
Cardiac Conduction Disease	CCD1	?	?	19q13-q13.3	AD	113900	CCD: ?	L				PM*
	CCD2	SCN5A	Nav1.5	3p21	AD	113900		M/L				PM*
	CCD3	?	?	16q23-q24	AD	5		L				PM*
	CCD4	EMD	STA	Xq28	XLD	6		M/L		AF/CMP	EDMD^	*
Familial Atrial Fibrillation	FAF1	?	?	10q22-q24	AD	608583	FAF: ?	L				AAD/ACO
	FAF2	KCNQ1	KVLQT1	11p15.5	AD	607554		M/L				AAD/ACO
	FAF3	?	?	6q14-q16	AD	608988		L				AAD/ACO
	FAF4	KCNE2	MiRP1	21q22.1-q22.2	AD	607554		M/L				AAD/ACO
	FAF5	KCNJ2	Kir2.1, IRK1	17q23.1-q24.2	AD	7		M/L				AAD/ACO
Cardiomyopathies												
Hypertrophic cardiomyopathy	CMH1	MYH7	MYHCB	14q11.2-q12	AD	160760	HCM: 1:500	M/L	c) 65%			*
	CMH2	TNNT2	c trop T	1q32	AD	115195		M/L				ICD
	CMH3	TPM1	TMSA	15q22	AD	11516		M/L				*
	CMH4	MYBPC3	MYBP-C	11p11.2	AD	115197		M/L				*
	CMH5	?	?	?	AD	115198		I				*
	CMH6	PRKAG2	AMPK-γ2	7q36	AD	600858		M/L		WPW/CD		*
	CMH7	TNNI3	TNNC1	19q13.2-13.3	AD	191044		M/L				*
	CMH8	MYL3	MLC3	3p21.2-21.3	AD	608751		L				*
	CMH9	TTN	titin	2q31	AD	188840		L				*

	CMH10	MYL2	MLC2	12q23-24.2	AD	608758		L				*
	FHC10	ACTC	alpha actin	15q14	AD	102540		L				*
	FHC11	MYLK2	MLCK	20q13.3	AD	606566		L				*
	FHC12	MYH6	MYHCA	14q12	AD	160710		L		CHD		*
	Noonan	PTNP11	PTP2C, SHP2	12q24.1	AD	163950	NS: 1:2,500	M/L	c)50%	CHD	##	*
	Fabry	GLA	GALA	Xq22	XLR	301500	F♂: 1:40,000 F♀:?	M/L	c)100%	HCM only in ♀♀	###	EZ
	Danon	LAMP2	LGP110	Xq24	XLD	300257	Danon: ?	M/IL			####	*
Dilated cardiomyopathy	CMD1A	MYBPC3	MYBP-C	11p11.2	AD	115200	DCM: >1:3000	M/L	c)10%			BB/AC/ICD*
	CMD1A	ACTC	alpha actin	15q14	AD	115200		L				BB/AC/ICD*
	CMD1A	MYH7	MYHCB	14q11.2-q12	AD	115200		M/L				BB/AC/ICD*
	CMD1A	LMNA	LMNC	1q21.2	AD	115200		M/L			LGMD^^, lipdystrophy	BB/AC/ICD*
	CMD1A	PLN	PLB	6q22.1	AD	115200		L				BB/AC/ICD*
	CMD1B	?	?	9q13	AD	600884		L				BB/AC/ICD*
	CMD1C	?	?	10q21-q23	AD	601493		L		MVP		BB/AC/ICD*
	CMD1D	TNNT2	c trop T	1q32	AD	601494		M/L				BB/AC/ICD*
	CMD1E	?	?	3p25.p22	AD	601154		L		SS,SVT		BB/AC/ICD*
	CMD1F	?	?	6q23	AD	602067		L		CD	LGMD^^	BB/AC/ICD*
	CMD1G	TTN	titin	2q24.3	AD	604145		L				BB/AC/ICD*
	CMD1H	?	?	2q14-q22	AD	604288		L				BB/AC/ICD*
	CMD1I	DES	desmin	2q35	AD	604765		L			muscle weakness	BB/AC/ICD*
	CMD1J	?	?	6q29.q24	AD	605362		L				BB/AC/ICD*
	CMD1K	?	?	6q12-q16	AD	605582		L				BB/AC/ICD*
	CMD1L	SGCD	DAGD	5q33	AD	606685		M/L				BB/AC/ICD*
	CMD1M	CSRP3	MLP	11p15.1	AD	607482		L				BB/AC/ICD*
	CMD1N	TCAP	TELE	17q12	?	607487		N				BB/AC/ICD*
	CMD1O	ABCC9	SUR2	12p12.1	AD	608569		L				BB/AC/ICD*
	CMD3A	TAZ	G4.5	Xq28	XLR	300069		M/L		NC,FE		BB/AC/ICD*
	FDC1	?	?	2q11-q22	?	8		I		CD		BB/AC/ICD*
	FDC2	?	?	19q13.2	AD	8		L		CD		BB/AC/ICD*
	FDC3	SCN5A	Nav 1.5	3p21	AD	9		M/L				BB/AC/ICD*
	ACMP/ASSS	SCN5A+CX40	Nav1.5+GJA5	3p21+1q21.1	DG	108770/10		M/L		CD		BB/AC/ICD*
	XLCM	DMD	BMD	Xp21.2	XLR	302045		M/L		♂♂>>♀♀		BB/AC/ICD*
	CMDmito	tRNA	MTTI	mt DNA	M	510000		M			muscle weakness	BB/AC/ICD*
Arrhythmogenic Right Ventricular Dysplasia	ARVD1	?	?	14q23-q24	AD	107970	ARVD: 1:5000	L	c)40%			BB/AC/ICD*
	ARVD2	RYR2	c ryanodine rec 2	1q41.2-q43	AD	600996		M/L				BB/AC/ICD*
	ARVD3	?	?	14q12-q22	AD	602086		L			muscle weakness	BB/AC/ICD*
	ARVD4	?	?	2q32.1-q32.3	AD	602087		L		CD		BB/AC/ICD*
	ARVD5	?	?	3p21.3-p23	AD	604400		L				BB/AC/ICD*
	ARVD6	?	?	10p14-p12	AD	604401		L				BB/AC/ICD*
	ARVD7	?	?	10q22.3	AD	609160		L		SSS		BB/AC/ICD*
	ARVD8	DSP	DPI, DPII	6p24	AD	607450		L				BB/AC/ICD*
	ARVD9	PKP2	plakophylin 2	12p11	AD	609040		M/L				BB/AC/ICD*
	Carvajal	DSP	DPI, DPII	6p24	AR	605676		L			#####	BB/AC/ICD*
	Naxos	JUP	junction plakoglobin	17q21	AR	601214		L			#####	BB/AC/ICD*

Table 1. Legend

A AD=autosomal dominant, AR=autosomal recessive, DG=digenic, XLD=X-linked dominant, XLR=X-linked recessive, M=maternal, C=compound, DN=de novo

B Reference number in OMIM database

C Reference if no OMIM number exists:

1) Brugada R, Hong K, Dumaine R et al. Circulation 2004;109 :30-5
2) Belloq C, van Ginniken AC, Bezzina CR et al. Circulation 2004;109:2394-7
3) Priori SG, Pandit SV, Rivolta I et al. Circulation Research 2005;96:800-7
4) Weiss R, Barmada MM, Nguyen T et al. Circulation 2002;105:707-13
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6) Sakata K, Shimizu M, Ino H et al. Circulation 2005;111: 3352-3358
7) Xia M, Jin Q, Bendahhou S et al. Biochem Biophys Res Commun. 2005 ;15;332:1012-9.
8) Seidman JG, Seidman C. Cell 2001;104 :557-67
9) McNair WP, Ku L, Taylor MR et al. Circulation 2004;110(15):2163-7
10) Groenewegen WA, Firouzi M, Bezzina CR et al. Circ Res 2003;92(1):14-22

D Estimated phenotypic prevalence of all subtypes of the diseases mentioned

E Current (2005) possibilities of diagnostic molecular testing in the Netherlands: M/L=mutation analysis/linkage studies if applicable, L=linkage studies, in large families only, N=not offered, I=impossible

F a) In familial cases (>1 affected individual and/or a family history with young unexplained sudden death), all subtypes (Hofman N, van Langen IM, Tan HL, Wilde AAM. Neth Heart J 2005;13: 8)
b) In isolated cases, all subtypes (idem)
c) In all cases referred for molecular testing, all subtypes

G A=atrial fibrillation, CD=conduction disorder, CHD=congenital heart defects, FE=fibroelastosis, MVP=mitral valve prolaps, NC=ventricular non-compaction, SS=sick sinus syndrome, SVT=supraventricular tachycardia, VT=ventricular tachycardia, WPW=Wolf-Parkinson-White syndrome

H # periodic paralysis, short stature, low set ears, hypoplastic mandible, hypotelorism, clinodactyly
retarded growth, abnormal facies, neck webbing, cryptorchism, pectus catinatum, funnel chest
angiokeratomas, acroparesthesias, hypohydrosis, corneal and lenticular opacities, renal insufficiency, stroke
####proximal muscle weakness, mental retardation
palmoplantar keratoderma, woolly hair
^ Emery Driefuss Muscular Dystrophy
^^ Limb Girdle Muscular Dystrophy

I AAD=anti-arrhythmic drugs, AC=ACE-inhibitors, ACO=anti-coagulation, BB=beta-blockers, RL=rules of living, ICD=internal cardiac defibrillator, EZ=enzyme-replacement, NN=none needed, Q=quinidine, U=unknown, *=dependent on phenotype

Table 2. Revised Clinical Criteria for diagnosis of the Long QT Syndrome

Characteristics	**Points**
Electrocardiographic findings [1]	
a. QTc	
>480 msec [1,2]	2
460-470 msec [1,2]	3
450 msec (in males) [1,2]	2
b. Torsade de pointes [3]	1
c. T-wave alternans	2
d. Notched T wave in the three leads	1
e. Low heart rate for age [4]	1
	0.5
Clinical history	
a. Syncope	
With stress	2
Without stress	1
b. Congenital deafness	0.5
Family history [5]	
a. Family members with LQTS	1
b. Unexplained sudden death at age <30 among immediate relatives	0.5

1. In the absence of medications or disorders known to affect these ECG features
2. The QT value is corrected for heart rate by using the Bazett formula: QTc= QT/√RR, where RR indicates heart rate
3. Mutually exclusive
4. Resting heart rate below the second percentile for age
5. The same family cannot be counted in a and b

Adapted from Schwartz PJ et al 1993 [4].

Table 3. (Dutch) Medication to be avoided by Long QT Syndrome carriers

Antiarrhythmics
kinidine, procaïnamide, disopiramide, sotalol, amiodarone, lidoflazine, mexiletine, flecaïnide, aprindine and bepridil

Antipsychotics and antidepressant drugs
chloorpromazine, haloperidol, imipramine, amitriptyline, nortriptyline, maprotyline, thioridazine, trifluorperazine and fluoxetine

Antibiotics
ampicilline, erytromycine, spiramycine, trimethoprim (bactrimel), pentamidine, ketoconazol

Antimalaria drugs
chloroquine, hydroxychloroquine

Other
terfenadine, astemizol, ketanserin, terodiline, probucol, doxorubicine and cisapride, diuretics (can be used when electrolytes are monitored)

When carriers (of a familiar mutation and/or an abnormal ECG) are identified, regular cardiologic evaluations are required to assess the risk of ventricular arrhythmias. Based on these risk assessments prophylactic treatment can be started or adjusted. In most cases daily treatment with beta blockers suffices. In the LQTS types 1 and 2 an internal cardiac defibrillator with or without pacemaker function (ICD) may occasionally be needed, in the LQTS type 3 this currently appears the only safe treatment. Prophylactic treatment has to start well before life-threatening symptoms can be expected, depending on age and clinical assessment. In LQTS1 this is long before the age of 5, in LQTS2 at 8 and in LQTS3 at the start of puberty. In asymptomatic carriers with a normal ECG above the age of 40, prophylactic treatment may not be necessary. All carriers need to avoid QT-prolonging drugs (Table 3). Also, in LQTS1 and LQTS2, carriers are advised to avoid gene-specific triggering situations like participation in (competition) sports, loud noises, anxiety and swimming and diving. Fever, nausea and diarrhoea should be medically treated in early stages, because arrhythmias may be triggered by changes in serum electrolyte concentrations and body-temperature, while prophylactic drug serum concentrations may temporarily not be reached. Close relatives of LQTS-patients are advised to learn resuscitation techniques. The pressure for full compliance (because forgetting to take the drugs for some days may trigger arrhythmias in particular), the side-effects of the beta-blockers, the complications of ICD's and these rules of living represent a heavy burden to all involved, especially to children and their parents (Table 4).

Table 4. Possible side effects of beta blockers*

Cold extremities, dyspnoea, provocation of bronchospasms, hypotension, tiredness, dizziness, headaches, visual problems, impotence, conduction disorder, depression, nightmares, rash, dry eyes, increased sensitivity to allergens, masking of hyperthyroidism and hypoglycaemias

*http://www.cvzkompassen.nl/fk/

2. Familial Cathecholaminergic induced polymorphic ventricular tachycardia (CPVT)

CPVT is a another arrhythmogenic disease, manifesting with exercise- or stress-induced polymorphic ventricular arrhythmias, syncope, seizures and sudden death, mainly at young age. It was described for the first time by Coumel in 1978 [10]. CPVT is inherited as an autosomal dominant or autosomal recessive trait, usually with high penetrance. The autosomal dominant form is caused by mutations of the cardiac ryanodin receptor gene (RyR2), the autosomal recessive form by mutations in the calsequestrin 2 (CASQ2) gene [11,12,13]. The proteins encoded by these genes have functions in the calcium-handling of cardiomyocytes, which is under the control of, among others, catecholamines. More genes may be involved. Both types occur in the Netherlands, with the autosomal dominant being far more prevalent. In 86% of familial CPVT cases a mutation can be found [14]. The true prevalence is still unknown, but will probably be less than that of the LQTS. In CPVT the resting-ECG is normal, which hampers an easy cardiologic diagnosis. Ventricular arrhythmias are only revealed at increased heart rates, during exercise-testing or on holter-monitoring. Prophylactic treatment with beta blockers is

usually effective in suppressing severe ventricular arrhythmias; in severe cases ICD-implantation may nevertheless be needed.

3.Brugada syndrome (BS)

The BS, described for the first time in 1992 by the Brugada-brothers, is another autosomal dominantly inherited disease characterised by ventricular arrhythmias and sudden death [15]. Death occurs mostly at rest (sleep) and the ECG-pattern resembles that of patients with acute myocardial infarction, with ST-segment elevation, particularly in leads V1-3. Conduction disturbances (among others right bundle branch block) are common as well. The typical ECG-pattern can be elicited by infusion of sodium-channel blockers (flecainide, ajmaline) in asymptomatic mutation carriers or survivors of ventricular fibrillation [16]. Fever may trigger symptoms. Sudden death most frequently affects males from 30 to 40 years, but may occur in all (adult) mutation carriers and in rare cases in children, particularly in triggering situations (e.g. fever). In up to 30% of cases a mutation in the SCN5A gene (also the LQTS3 gene) can be found [17]. SCN5A mutations in LQTS3 lead to gain of function of the sodium channel, while in BS mutations give rise to loss of function. The BS is a genetically heterogeneous disease, with a second locus on 3p22-25, but more causal genes or loci have not been identified yet [18]. In a large Dutch family the occurrence of LQTS3 as well as BS and conduction disease caused by the same SCN5A mutation was described [19]. Families with isolated conduction disorder caused by mutations in the SCN5A gene have also been published, as well as several other families in which combinations of the three possible SCN5A-caused phenotypes segregate. The prevalence of BS is estimated at 1 in 10.000 in South-East Asia and Japan. In the western world, including the Netherlands, the prevalence must be much lower, but still has to be determined. Prophylaxis of sudden death is currently only possible by ICD-implantation.

4. The short QT syndrome (SQTS)

The short QT syndrome is a newly described clinical entity characterized by the presence of a short QT interval associated with cardiac tachyarrhythmias including sudden cardiac death at a young age in otherwise healthy individuals. A genetic basis has been identified linking the disease to (gain of function) mutations in KCNH2 (SQTS1) and KCNJ2 (SQTS3) in the familial forms and a mutation in KCNQ1 (SQTS2) in a sporadic form of the disease [20,21,22]. The prevalence is unknown. Effective therapy consists of ICD implantation and probably of quinidine medication.

5. Familial Atrial Fibrillation (FAF)

Atrial fibrillation is the most common sustained cardiac rhythm disturbance, with an overall prevalence of 0.89%. The prevalence increases rapidly with age, to 2.3% between the ages of 40 and 60 years, and to 5.9% over the age of 65. The complication most feared is thromboembolic stroke. In 15-30% of patients an underlying (cardiac) disease is absent. This condition is called lone AF. The monogenic familial form of atrial fibrillation is probably less rare than previously recognized, as 15% of patients with lone AF are reported to have a positive family history. Three chromosomal loci and the KCNQ1 and KCNE2 genes are associated with FAF. Recently,

a gain-of-function mutation in the KCNJ2 gene has been proven to cause FAF in one of thirty investigated Chinese kindreds [23,24].

6. Sick Sinus Syndrome (SSS)

The term 'sick sinus syndrome' encompasses a variety of conditions caused by sinus node dysfunction. The most common clinical manifestations are syncope, presyncope, dizziness, and fatigue. The electrocardiogram typically shows sinus bradycardia, sinus arrest, and/or sinoatrial block. Episodes of atrial tachycardias coexisting with sinus bradycardia ('tachycardia-bradycardia syndrome') are also common in this disorder. SSS occurs most often in the elderly associated with underlying heart disease or previous cardiac surgery, but can also occur in the fetus, infant, or child without heart disease or other contributing factors, in which case it is considered to be a congenital disorder. Familial SSS is often accompanied by atrioventricular conduction disturbance. Mutations in the SCN5A gene cause an autosomal recessive form of SSS. An frameshift mutation in the HCN4 gene was identified in an isolated SSS-patient [25,26].

7. Familial Conduction Disease (CCD)

Progressive familial heart block is an autosomal dominantly inherited cardiac bundle branch disorder that may progress to complete heart block. CCD type I is defined on electrocardiogram by evidence of bundle branch disease. Progression has been shown from a normal electrocardiogram to right bundle branch block and subsequently to complete heart block. These electrocardiographic features differentiate PFHBI from progressive CCD type II, in which the onset of complete heart block is associated with narrow complexes. CCD is manifested symptomatically when complete heart block supervenes, either with dyspnea, syncopal episodes, or sudden death. Treatment, which is best managed by regular electrocardiographic follow-up, is by implantation of a pacemaker. Two chromosomal loci and the SCN5A gene are associated with autosomal dominant forms of CCD [27,28,29].

8. Atrial standstill syndrome (ASSS, ACMP).

Atrial standstill is a rare arrhythmogenic condition characterized by the absence of electrical and mechanical activity in the atria, transient or persistent, and complete or partial. It can be "idiopathic", sporadic or familial, or secondary to Ebstein's anomaly, Emery-Dreifuss muscular dystrophy (X-linked), Kugelberg-Welander syndrome (autosomal recessive), and amyloidosis. Idiopathic familial atrial standstill is inherited as autosomal dominant trait with variable penetrance. The diagnosis relies on the ECG demonstration of bradycardia, absence of P waves, and junctional narrow complex escape rhythm. The treatment is addressed to the thromboembolic risk, mitral incompetence and syncope. In a large Dutch family with ASSS and low penetrance, expression of disease was associated with the concurrence of a cardiac sodium channel mutation and rare polymorphisms in the atrial-specific Cx40 gene. We propose that, although the functional effect of each genetic change is relatively benign, the combined effect of genetic changes eventually progresses to complete ASSS [30,31].

Cardiomyopathies

1. Hypertrophic cardiomyopathy (HCM)

According to the definition of the World Health Organisation HCM is characterized by unexplained left and/or right ventricular hypertrophy, which is usually asymmetric and involves the interventricular septum [32]. The disease was first described in 1958 by Teare. With an estimated prevalence of 1:500 is HCM the most prevalent monogenic disease of the myocardium. It is the most common cause of sudden unexpected cardiac death in young people, including competitive athletes. Sudden death from ventricular arrhythmias, ischemia or outflow tract obstruction may occur at any age, but is most prevalent in individuals 30 years of age or less. Symptoms of HCM are dyspnoea, angina pectoris, syncope, atrial and ventricular arrhythmias, sudden death, thrombo-embolic events and heart failure.

Diagnosis is established by ECG- and echocardiographic studies, sometimes by cardiac magnetic resonance (CMR) studies. The pathological signature is myocardial disarray.

The individual risk of sudden death in the individual with HCM or carrying a HCM mutation (approximately 1% in low risk symptomatic patients, up to 5% in high risk patients) can be estimated by the use of clinical criteria, including family data (Table 5). Prophylaxis of sudden death in high risk patients is only possible by the use of an ICD, other clinical complaints can be treated with medication and/or invasive treatments (septum reduction).

Table 5. Risk factors for sudden cardiac death in Hypertrophic Cardiomyopathy*

Risk factor	**Criterion**
Nonsustained ventricular tachycardia (NSVT)	Multiple and repetitive or prolonged burst of NSVT on holter monitoring
(Near) Syncope	During exercise and/or recurrent, and/or arrhythmia-based, and/or unrelated to neurocardiogenic mechanisms, and/or in young patients
Exercise blood pressure response (BPR)	Hypotensive response, in patients ≤ 50y
Family history of sudden death	In close and/or multiple relatives
Left ventricular wall thickness (LVWT)	≥ 30mm, particularly in adolescents and young adults

*Adapted from: Barry J. Maron. Hypertrophic Cardiomyopathy: A Systematic Review JAMA 2002; 287: 1308-1320.

HCM is an autosomal dominantly inherited disease. At present 12 mutant genes are associated with the HCM phenotype. Most genes code for proteins involved in the function of the sarcomere. DNA-testing in the Netherlands is performed for the 5 sarcomeric genes that are affected most often (MYBPC3, MYH7, TNNT2, TNNI3, TPM1) and for mutations in two non-sarcomeric genes (PRAKG2, GLA), associated with HCM and the Wolf Parkinson White syndrome and with Fabry disease respectively. In relatively frequent forms of syndromic HCM, the Noonan syndrome and the X-linked Danon syndrome, DNA-testing (PTNP11 and LAMP2 genes) is also possible [33,34].

The cardiac myosin binding protein C gene (MYBPC3) and the beta myosin heavy chain gene (MYH7) are involved in approximately 64 and 10 percent of genotyped HCM-families in the Netherlands respectively. In 23% of families one founder mutation is responsible; the 2373 ins G mutation in the MYBPC3 gene. This mutation must have been present in a Dutch founder around the year 1200 and spread over the country, with the highest prevalence in 'West-Friesland' [35]. At least three other founder mutations in MYBPC3 segregate in the Netherlands. After discovery of these mutations in 2002, DNA-testing in HCM became relatively easy and quick.

Mutations in the MYBPC3 gene are associated with delayed penetrance (after puberty) and in the MYH7 gene with penetrance and sudden death at young age (from puberty), but exceptions exist. The mean interventricular septum thickness seems to be larger in families with MYH7 mutations than in those with MYBPC3 mutations. The cardiac troponin T (TNNT2) gene is associated with HCM with mild or no hypertrophy in conjunction with a high risk of sudden death due to ventricular arrhythmias. Further genotype-phenotype correlations cannot be made yet.

2. Dilated cardiomyopathy (DCM)

Adult onset idiopathic (non-ischemic and not associated with neuromuscular or other systemic disorders, such as amyloidosis) DCM is an inherited disease in at least 35% of cases. More than in the other cardiogenetic diseases DCM can be a systemic disease, with functional and structural aberrations in the skeletal muscles (not leading to complaints in most cases) as well. In 10% of cases HCM finally evolves into DCM. All cause DCM has a prevalence of 36.5 in 100.000, the contribution of monogenic forms of the disease is not clear [36,37].

Hallmarks of the disease are systolic and diastolic ventricular and atrial dysfunction, in conjunction with impaired pumping capacity. The development of intracardiac thrombi may lead to thrombo-embolic events. Other symptoms are dyspnoea, reduced exercise tolerance, palpitations, syncope, angina pectoris and heart failure. Sudden death due to ventricular arrhythmias may occur. Diagnosis is possible by ECG-testing and echocardiography, with exercise- and holter-testing to estimate the risk of arrhythmias. The pathological picture is non-specific. Treatment of DCM is mostly symptomatic, and consists of drugs, ICD-implantation in selected cases, and cardiac transplantation in case of severe heart failure. ACE-inhibitors have been proved to slow disease-progression in ischemic DCM and may also be of use as prophylaxis in idiopathic (genetic) DCM, in symptomatic patients and perhaps also in still asymptomatic mutation carriers. Idiopathic adult onset DCM is an autosomal dominant disease in most cases, but may be inherited in an X-linked recessive and mitochondrial way as well. As in other cardiogenetic diseases penetrance is reduced and expression varies between and within families. Many mutated genes can be responsible for the DCM phenotype [38].The genes code for proteins that form the cytoskeleton or the sarcomere (the same genes giving rise to HCM in other families). X-linked forms of DCM are caused by certain mutations in the dystrophin gene (DMD) and the G4.5 or taffazine gene (TAZ). This last gene is associated with the phenotypes of non-syndromic noncompaction cardiomyopathy and endocardial fibroelastosis and with Barth syndrome [39,40]. Most of the genes mentioned above are mutated very rarely. The

gene currently most often reported to be mutated in DCM is the Lamin A/C gene (LMNA) [41]. Mutations in this (nuclear envelope) gene lead to autosomal dominant DCM associated with conduction disturbances and a high risk of sudden death. Carriers of a mutation in this gene are advised to be treated with an ICD therefore [42].

DNA-testing in DCM is still in the research phase, except for LMNA screening. Family screening therefore still usually relies on cardiologic testing. The help of a neurologist, specialised in neuromuscular disorders is useful too, regarding the possible involvement of the skeletal muscular system.

3. Arrhythmogenic Right Ventricular Dysplasia or Cardiomyopathy (ARVD/ARVC)

ARVD was first described as clinical entity in 1978 by Fontaine. It is defined as 'total or partial replacement of right ventricular muscle by adipose and fibrous tissue associated with arrhythmias of left bundle branch block configuration'. Diagnosis is made by ECG-, (contrast) echocardiographic and magnetic resonance imaging (MRI)-studies, sometimes by pathological studies of a myocardial biopsy. The main risk in ARVD is that of sudden death due to ventricular arrhythmias in young persons (<35y) particularly in those not yet aware of this diagnosis. Heart failure is reported less often, but leads to cardiac transplantation in some patients. ICD implantation is an effective treatment in high-risk patients, but medication and catheter ablation can also be applied in eligible cases.

The prevalence of ARVD is estimated at 1 in 5000 in most western countries, but this must be an underestimation because of the missed diagnosis in a substantial number of patients (sudden death victims). Males are clinically affected more often than women [43].The mode of inheritance is autosomal dominant in non-syndromic forms, the low penetrance in many families adds to the difficulties in diagnosis. Syndromic forms (Naxos disease), associated with woolly hair and/or palmoplantar keratoderma (and also with DCM in Carvajal disease) are autosomal recessively or dominantly inherited and caused by mutations in the plakoglobin (JUP) and desmoplakin (DSP) genes [44,45,46].

Until now three genes are associated with non-syndromic ARVD: the desmoplakin gene, the plakophylin (PKP2) gene and the cardiac ryanodin receptor gene (RYR2), also responsible for CPVT. Also 9 DNA-loci are associated with ARVD, which implies that many genes still have to be identified [47]. DNA-testing in ARVD patients currently leads to a molecular diagnosis in a minority (up to 40%) of cases. Most genotyped patients in the Netherlands have PKP2 mutations.

Sudden unexplained death (SUD)

Sudden, unexplained, death (SUD) of one or more young relative(s) (<40-45y) has increasingly become a reason for referral to the cardiogenetics outpatient clinic. In these cases the point of departure is not the suspicion or knowledge of a certain cardiogenetic disease in a living patient complaining of symptoms, but the fact that sudden death could have been a manifestation of one of all genetic diseases mentioned in the first part of this chapter, therefore implying a risk to relatives. Sudden death is mostly caused by structural cardiac disorders which ultimately result

in lethal ventricular arrhythmias [48,49,50,51]. It accounts for up to 10,000 deaths annually in the Netherlands, and is responsible for 50% of mortality from cardiovascular disease. Only half of these victims was diagnosed with a heart disease before dying [52]. In individuals above 40 years of age, coronary artery disease is by far the most prevalent cause. In younger individuals, various other causes are predominant. If post-mortem studies do not provide an explanation, a primary electrical disease is the most likely cause of death, although ARVD still is a possibility, as the patchy fatty infiltration may easily be overlooked. When no post-mortem studies have been performed, cardiomyopathies, particularly HCM, are expected to be the most probable cause of death in the young (based on prevalences in cases where post-mortem studies have been performed). Primary arrhythmias, connective tissue diseases (e.g. Marfan's syndrome) and premature atherosclerotic disease (familiar dyslipidemias) are also possible. While post-mortem studies indicate that an estimated 60-75% of these young victims die from potentially inherited diseases, many sudden death cases remain unexplained [40,41]. These sudden unexplained death (SUD) cases pose a serious dilemma for the physicians involved, because the potential heritability of the underlying diseases puts surviving relatives at risk of sudden death, of which they are seldom aware. Although severe distress may be caused by revelation of these risks, the possibilities of prevention of recurrence of fatal events justify informing these relatives in our opinion. This confers urgency to the timely identification of the underlying disease (in order to design preventive treatment in relatives), by which the heritability of SUD may also be exploited. Given their usual autosomal dominant mode of inheritance, the underlying diseases may be identified by cardiologic workup in surviving relatives of SUD victims, even when no clues can be obtained from the history or post-mortem analysis of the deceased. At the same time, this analysis may unmask affected surviving relatives in whom the disease had remained unrecognized. [16,53,54]. Examination of relatives of young SUD victims has a high diagnostic yield (disease identification in 40%) and therapeutic yield in our centre (identification of 11.6 presymptomatic carriers/family). Simple procedures (examining as many close relatives as possible) and routine tests (resting/exercise ECG, echocardiography, holter-ECG, CMR where needed) constitute excellent diagnostic strategies when hypothesis driven (choice of cardiologic investigations based on the most likely diagnoses in the individual case). Molecular genetics provide strong supportive information [55]. When no diagnosis is reached despite extensive cardiologic studies in all close relatives, children (under 18) of the deceased person are still at a non-trivial risk for a cardiogenetic disease with penetrance in later life. Regular cardiologic follow up seems to be indicated

B. Diseases associated with familiar sudden cardiac death, but currently not investigated in the cardiogenetic outpatient clinic

1. Marfan syndrome and heritable forms of aorta dissection

Marfan syndrome is a connective tissue disorder with autosomal dominant inheritance caused by a defect in the fibrillin gene on chromosome 15 [56,57]. The expression varies. Patients may have tall stature, abnormal body proportions, ocular abnormalities, dural ectasia,

protrusio acetabulae, and present with skeletal and cardiovascular abnormalities. Mitral valve prolapse with mitral regurgitation, ascending aortic dilation/aneurysm with subsequent aortic regurgitation, and aortic dissection (leading to sudden death in the majority of cases) are the most common cardiovascular abnormalities [58]. Regular cardiovascular follow up, treatment with beta-blockers and elective aortic surgery prevent sudden death at young age in most cases. Prevalence is estimated at 1 in 5000.

Familial, autosomal dominant, forms of aorta dissection are recognised as well. Loci at 11q (FAA1), 5q (FAA2), 3p (FAA3) are identified, but sofar no causal genes have been cloned.

Ehlers-Danlos syndrome type IV (vascular type) is an autosomal dominant connective tissue disorder characterized by a characteristic facial appearance, translucent skin, hypermobile joints and dermal manifestations as in other forms of the syndrome (not predisposing to sudden death) but typically patients show spontaneous rupture of intestines and large arteries. Mutations in the COL3A1 gene are causative [59].

2. Familial hypercholesterolemia and other heritable hyperlipidemias

Familial hypercholesterolemia (FH) is an autosomal dominantly inherited genetic condition, caused by mutations in the LDLR gene, that usually results in markedly elevated LDL (low-density lipoprotein) and total cholesterol levels beginning at birth, and resulting in cardiovascular (atherosclerotic) disease at relatively early age. Typically in affected men, myocardial infarctions (with sudden death in many of them) occur in their 40s to 50s, and 85% of men with this disorder have experienced a heart attack by age 60. The incidence of myocardial infarctions in women with this disorder is also increased, but delayed 10 years compared to men. Homozygous FH leads to coronary artery disease at very young age. Heterozygote frequency is approximately 1 in 500 in western Europe. Mutation analysis in the Netherlands is simple for 9 common LDLR mutations which are responsible for FH in 66.5% of index cases [60]. FH is, less frequently, caused by mutations in the APOB and PCSK9 genes. Statin therapy has proven useful in the treatment of FH. Maximum health benefit can be obtained in FH if treatment is started as early as possible, as the World Health Organization has recently recommended. In the Netherlands case-finding and family screening is performed by the StOEH (see below) Since its initiation, the program identified more than 6000 individuals with FH, of whom the greatest part was not adequately treated at the time of identification [61]. Unfortunately, compliance with prophylactic treatment after identification in this setting is still reported to be a problem [62].

Familial combined hyperlipedemia (elevation of both cholesterol and triglycerides, USF1 gene and locus at chromosome 11p) and familial hypertriglyceridemia (APOA5, LIPI genes), are other forms of heritable hyperlipidemias predisposing to sudden death due to premature coronary artery disease.

3. Monogenic diseases predisposing to sudden death due to coronary artery disease

Monogenic forms of essential hypertension and mutations or polymorphisms leading to hyperhomocysteinemia also may predispose to premature coronary artery disease. Systematic screening of eligible patients for these predispositions is not yet performed, nor is family screening.

4. Prevalent heritable neurological diseases associated with premature sudden cardiac death

-Myotonic Dystrophy

Recently it has become clear that Myotonic Dystrophy leads to premature sudden cardiac death in relatively many carriers of the disease gene [63,64,65]. Myotonic dystrophy (dystrophia myotonica, DM) is the most frequently inherited neuromuscular disease of adult life. DM is a multisystem disease with major cardiac involvement. Core features are myotonia, muscle weakness, cataract, and cardiac conduction abnormalities. Classical DM (first described by Steinert and called Steinert's disease or DM1) is an autosomal dominant disorder associated with the presence of an abnormal expansion of a CTG trinucleotide repeat on chromosome 19q13.3 (the DM 1 locus). While 5-34 CTG repeats are observed in normal alleles, their number may reach 50–2000 in DM1. A similar but less common disorder was later described as proximal myotonic myopathy, caused by alterations on a different gene on chromosome 3q21 (the DM2 locus). During a 10 year follow up study of 367 DM1 patients, mortality was 7.3 times of that of an age matched reference population, with a mean age at death of 53 years and a strong association between age at onset of DM1 and age of death. In this series, respiratory failure and cardiovascular disease were the most prevalent causes of death, accounting for about 40% and 30% of fatalities, respectively. Cardiac mortality occurred because of progressive left ventricular dysfunction, ischemic heart disease, pulmonary embolism, or as a result of unexpected sudden death. Relative contribution of sudden death ranges from about 2–30% in different published series, according to selection criteria. The hypothesis that cardiac arrhythmias may represent the most prevalent cause of sudden death in DM1 patients is supported by the absence of other causes of sudden death at necropsy studies. Sudden cardiac death may be caused by ventricular asystole, ventricular tachycardia (VT), ventricular fibrillation (VF) or electromechanical dissociation. The consistent evidence of the degeneration of the conduction system in DM generated the hypothesis that bradyarrhythmias might represent the most prevalent mechanism of SD. However, ventricular tachyarrhythmias are increasingly recognised as a common finding in these patients, possibly explaining cases of sudden death after pacemaker implant. Endomyocardial biopsies and postmortem studies performed on patients with DM1 have documented various degrees of non-specific changes, such as interstitial fibrosis, fatty infiltration, hypertrophy of cardiomyocytes, and focal myocarditis. A selective and extensive impairment of the conduction system is the most common finding. Cardiologic surveillance of Myotonic Dystrophy patients is currently not systematically performed in the Netherlands and many mutation carriers are not aware of their genetic status let alone of their risk of sudden death. Active cascade screening for Myotonic Dystrophy is not customarily offered each time an index patient is identified.

-Duchenne and Becker muscular dystrophy (DMD and BMD)

DMD and BMD are X-linked recessive diseases leading to dystrophy of skeletal and cardiac musculature in affected males. The DMD/BMD-gene on chromosome Xp21.2 encodes the protein dystrophin. The prevalence rate at birth of DMD in the Netherlands is estimated at 1:4215 male live births yearly [66]. Affected males are at considerably increased risk of heart failure and (sudden) death due to (dilated) cardiomyopathy, regular cardiologic follow up and treatment are therefore indicated in all affected males.

Female carriers, sometimes not aware of their status, are also at risk for cardiac abnormalities. Signs and symptoms of DMD and BMD were studied among confirmed Dutch carriers by Hoogerwaard et al. They showed that 19% of DMD-carriers and 16% of BMD-carriers had left ventricular dilatation and 8% of DMD-carriers had dilated cardiomyopathy (mean age 39.6y), independent from skeletal muscle involvement. The majority had no complaints [67,68]. It is likely that female carriers are at increased risk for heart failure and premature death. Epidemiological studies are needed to confirm this. If this is indeed the case, timely identification, cardiologic surveillance and prophylactic treatment are indicated on medical grounds. An European Neuromuscular Centre Working Group of knowledgeable neurologists and cardiologists currently advises to screen carriers for cardiologic symptoms at least every 5 years, from the age of 16. When significant cardiologic abnormalities are detected, ACE-inhibition should be considered [69].

C. Backgrounds of genetic counselling and genetic testing

1.Genetic counselling

-Background

Genetic counselling is usually defined as 'A communication process, which deals with human problems associated with the (risk of) occurrence of a genetic disorder in a family. In this process an appropriately trained professional (physician, genetic counsellor) should help an individual and/or his family to

-Comprehend the medical facts (disorder/diagnosis, course and management)

-Understand the heredity contribution to the disorder and recurrence risks (in relatives an for future children)

-Understand the options available for dealing with the recurrence risks (such as prenatal diagnosis and reproductive alternatives)

-Choose a course of action in view of their risks, compatible with family goals, values, religious beliefs, and act in accordance with that decision

-Make the best possible adjustment to the condition in an affected person and/or to the recurrence risk of the disorder'.

This often used definition dates back from 1975 [70]. The more recent definition of genetic counselling of the World Health Organisation (1998) is more general: 'The provision of accurate, full and unbiased information in a caring, professional relationship that offers guidance, but allows individuals and families to come to their own decisions' [71].

The value and effectiveness of genetic counselling services have been measured in several ways. Various studies have shown increased knowledge, lower costs as a result of more appropriate use of genetic tests, and higher rates of risk identification as some of the outcomes of genetic counselling services [72].

Genetic counselling as part of routine care is performed by many different medical specialists when treating patients with heritable disease or in the scope of a (planned) pregnancy. Primary care givers are involved with simple forms of genetic counselling as well. Nurses and social workers involved in the psychosocial care of people with chronic heritable

diseases or handicaps, are also providing genetic counselling in eligible situations.

Complex genetic counselling and counselling in 'acute' situations (e.g. during pregnancy) however is performed by clinical geneticists, or by genetic counsellors (supervised by clinical geneticists), at least in western countries having disposal of these professionals, like the Netherlands [73]. A clinical geneticist is a medical practitioner trained in the application of the principles of human genetics, including laboratory findings, to the diagnosis and management of genetic disorders and (supervision of) the counselling of patients and their families. Currently both professional groups are employed in academic centres (third echelon).

Genetic counselling is in general provided to patients with (possible) heritable diseases or (congenital) handicaps and/or mental retardation, their parents and their healthy relatives and to consanguineous couples or to couples in which one of the partners (usually the wife) is exposed to teratogeneous agents (drugs, irradiation). Genetic counselling can be diagnostic (in patients), presymptomatic or predictive (in healthy relatives) and be 'reproductive', that is aimed at estimating risks for offspring and at prenatal diagnostic options, if applicable. In the past genetic counselling predominantly was diagnostic or reproductive. Since the identification of genes predisposing to late onset heritable diseases (e.g. Huntington's disease, breast/ovary cancer, cardiogenetic diseases) predictive counselling accounts for more than 50% of patient care in academic clinical genetic centres.

To discuss issues on genetic counselling and testing and to produce recommendations from the professional point of view, the Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG) organized a workshop in September 2000 in Helsinki, Finland, to which 43 experts from 17 European countries were invited. Following the workshop, the PPPC issued statements and recommendations, which are expected to reflect the current views of the scientific and professional community in Europe (Table 6).

Table 6. ESHG statements and recommendations (1-21) on the provision of genetic services*

Aims and scope of genetic services

(1) The aim of a genetic service is to respond to the needs of individuals and families who are threatened by genetic disease, particularly their wish to know whether or not they are at risk of developing or transmitting a disorder with a genetic component.

(2) Genetic risks have two main components: the probability that a particular disorder will occur, and the burden that it can inflict. Genetic services deals with both.

(3) Genetic services should support the identification of and care for relatives who are at risk of serious genetic disorders, but who may not have been directly referred, so that they too may receive well-informed genetic counselling and guidance on preventive and therapeutic actions if required.

(4) Genetic services are characterized by the fact that diagnosis, investigations, counselling and support are given for disorders affecting any organ system at any age. Records are sometimes kindred based and multigenerational, which requires extra care in ensuring data protection.

(5) Genetic services comprise multidisciplinary groups of medical and non-medical disciplines such as, in the clinical setting, medical geneticists, psychologists, genetic counsellors, genetic nurses, and, in the laboratory setting, biologists, biostatisticians and specialized technicians.

(6) Clinical laboratory services that should be provided include cytogenetic, biochemical and molecular tests. They should have a close collaboration with the clinical services.

(7) At the community level, the services should include prenatal and newborn screening and follow-up, birth defects monitoring and follow-up, teratogen information services and outcome evaluation, genetic screening of selected populations, educational services for professionals and the general public, data collection and evaluation. These services may or may not be linked to family-focused genetic services.

Regulation and access

(8) Medical genetics should be recognized as a specialty.
(9) Genetic services should only be carried out under the responsibility of a duly qualified physician.
(10) Centres where laboratory tests are performed should be approved by the State or by a competent authority in the State, and the laboratories should participate in an external quality assurance scheme when available.
(11) There should be equality of access to genetic services, without financial considerations and without preconditions concerning the personal choices.
(12) The provision directly to the public of tests for diagnosing genetic diseases or a predisposition to such diseases, or for the identification of carriers of such diseases, should only be allowed subject to strict national licensing.

Consent, information and counselling

(13) The provision of genetic services should be based on respect for the principle of self-determination of the persons concerned. For this reason, any genetic testing, even when offered systematically, should be subject to their express, free and informed consent. No condition should be attached to the acceptance or the undertaking of genetic tests.
(14) The testing of the following categories of persons should be subject to special safeguards: minors, persons suffering from mental disorders and adults placed under limited guardianship. Testing of these persons for diagnostic purposes should be permitted only when this is necessary for their own health or if the information is imperatively needed to diagnose the existence of a genetic disease in family members.
(15) Genetic diagnosis in children and adolescents requires careful consideration of what is in their best interest. It is indicated if it is necessary for the differential diagnosis of manifest symptoms or for establishing the cause of a disease. A predictive genetic test is indicated during childhood if the onset of a disorder can be expected at this age and if medical measures can be taken to prevent the disease or its complications or to treat the disease. Other predictive tests and tests for carrier status should be delayed until the person is old enough to make an informed decision. Deviations from this rule may be acceptable in situations where knowledge of a healthy child's phenotype may contribute to establishing haplotype information that are of medical benefit to the other family members. Deferring genetic tests should not prevent discussing them with the child in a manner appropriate to his/her age.
(16) The psychological complexity of presymptomatic and predictive testing requires careful consideration. An adequate and systematic multidisciplinary approach as well as ongoing education of professionals and of the general public has been recommended to avoid pitfalls.
(17) Much of the counselling in relation to common problems such as an increased risk of chromosomal anomalies, and preliminary evaluation of the possibility of hereditary cancer in a family, can be performed by specifically trained non-physician healthcare providers or non-genetic specialist MDs in collaboration with genetic centres.
(18) Genetic counselling must be based on up-to-date knowledge of the disease, and the genetic counsellors should have the required capacities to help families to make decisions that are right for them and to make the best adjustment to their situation, while maintaining a 'nondirective' stance.
(19) Counselling should preferably be available in the individual's own language or, alternatively, interpreters should be used. In cases of complicated or detailed data, the information should also be provided in a written summary.
(20) In addition to genetic counselling and information given during a personal contact between the counsellor and the client, other ways of distributing information to patients and families should be used. These include books, leaflets, videos, websites and telemedicine approaches.
(21) Patients and families should be informed of existing patient support groups relevant to their problem.

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* Adapted from: Provision of genetic services in Europe: current practices and issues. European Society of Human Genetics. Eur J Hum Genet. 2003 Dec;11 Suppl 2:S2-4.

-Components of genetic counselling sessions

In order to achieve the objectives of genetic counselling mentioned before, five major components comprise the session(s):

a. Diagnosis

Collection of necessary information to confirm or establish the diagnosis/diagnoses in the patient and/or the family. Strategies to be utilised are e.g. taking a detailed (family) history and preparation of a pedigree, collection of medical and autopsy reports of family members, assessment of the counsellee.

Table 7. Ethical, Legal and Social (ELSI) aspects of testing and screening*

The U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) that devotes 3% to 5% of their annual Human Genome Project (HGP) budgets toward studying the ethical, legal, and social issues (ELSI) surrounding availability of genetic information. This represents the world's largest bioethics program, which has become a model for ELSI programs around the world. Topics that are being addressed, also being important regarding diseases predisposing to sudden death, are:

- **Fairness in the use of genetic information** by insurers, employers, courts, schools, adoption agencies, and the military, among others: Who should have access to personal genetic information, and how will it be used?
- **Privacy and confidentiality** of genetic information: Who owns and controls genetic information?
- **Psychological impact and stigmatization** due to an individual's genetic differences: How does personal genetic information affect an individual and society's perceptions of that individual? How does genomic information affect members of minority communities?
- **Reproductive issues** including adequate informed consent for complex and potentially controversial procedures, use of genetic information in reproductive decision making, and reproductive rights: Do healthcare personnel properly counsel parents about the risks and limitations of genetic technology? How reliable and useful is fetal genetic testing? What are the larger societal issues raised by new reproductive technologies?
- **Clinical issues** including the education of doctors and other health service providers, patients, and the general public in genetic capabilities, scientific limitations, and social risks; and implementation of standards and quality-control measures in testing procedures: How will genetic tests be evaluated and regulated for accuracy, reliability, and utility? How do we prepare healthcare professionals for the new genetics? How do we prepare the public to make informed choices? How do we as a society balance current scientific limitations and social risk with long-term benefits?
- **Uncertainties** associated with gene tests for susceptibilities and complex conditions (e.g., heart disease) linked to multiple genes and gene-environment interactions: Should testing be performed when no treatment is available? Should parents have the right to have their minor children tested for adult-onset diseases? Are genetic tests reliable and interpretable by the medical community?
- **Conceptual and philosophical implications** regarding human responsibility, free will vs genetic determinism, and concepts of health and disease: Do people's genes make them behave in a particular way? Can people always control their behaviour? What is considered acceptable diversity? Where is the line between medical treatment and enhancement?
- **Commercialization of products** including property rights (patents, copyrights, and trade secrets) and accessibility of data and materials: Who owns genes and other pieces of DNA? Will patenting DNA sequences limit their accessibility and development into useful products?

*Adapted from: http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml

b. Information
Explanation of disease facts, like diagnosis, natural history, prognosis, treatment and management modalities, genetic implications and possible options. Information on the ethical, legal and social (ELSI) aspects of testing (Table 7) and discussion of these facts and their perception by the counsellee.*c. Decision making and support*
Supporting and reinforcing of choices in couples wanting to raise a family or in individuals wanting predictive testing. Helping individuals and families to cope with the discovery of a genetic disorder in the family or in an individual. Guide the genetic testing-procedure, building in time for consideration of options in case of predictive testing.
d. Disclosure of test-results and referral (where appropriate)
Discussing the (predictive or diagnostic) test-results and the preventive or therapeutic options. Discussing (in carriers) the options for the testing of offspring. Referring to cardiologist and/or other medical specialist for further clinical testing, treatment and follow up.
e. Follow up
Sending a letter to the counsellee(s) summarizing the information given, encouraging people to pose questions or to return for follow-up session for further information or to discuss concerns or feelings (with the genetic counsellor or cardiologist or with a psychosocial worker). Encouraging (further) family screening (cascade screening) where appropriate and helping to organize this.

In the Netherlands, the maintenance of genetic registers and the long-term follow up of patients and counsellees are not viewed as professional responsibilities, contrary to the situation in the UK [74].

-Evidence based protocols and guidelines in genetic counselling
Evidence based guidelines in clinical genetics are still scarce, particularly regarding diagnostic and reproductive genetic counselling. Most existing guidelines are based on consensus. There is a growing body of literature considering genetic counselling services in a variety of clinical settings. This literature encompasses both predictive and diagnostic testing, from the viewpoints of service providers and recipients. It also embraces a wide range of conceptions of the nature and goals of genetic counselling. However, research in this area has been criticised for a focus on outcome rather than process, and it has been suggested that this focus limits its practical use [75].

With the identification of genes predisposing to incurable (neurologic) diseases, in the nineties of the last century, the need for guidelines strongly emerged however, in particular because patient organisations uttered their need for presymptomatic testing in healthy relatives of symptomatic patients.

The first disease in which presymptomatic DNA-testing became possible, is Huntington's disease. Since the late eighties of the last century, a predictive DNA-test, still based on linkage studies in extended families, became available. This test was carefully introduced because severe consequences of the test were anticipated, especially for persons receiving an increased risk outcome. In 1993, the detection of the CAG-repeat in the Huntington gene at chromosome 4 allowed direct mutation testing in individuals with more than 99% certainty.

Table 8. Outline of original genetic counselling guidelines for presymptomatic testing in Huntington's disease (using linkage)*

There are variations among countries and centres but the following represents some key elements of the basic protocol which has been followed since 1988, at least in the United States, Canada, the United Kingdom and the Netherlands:

1) There must be a minimum of three to six separate counselling sessions before diagnostic information is delivered. Each session should be several hours long. Intensive counselling regarding motivations and preparation for testing is the most essential element of the entire protocol. Post-test counselling must be part of any protocol but clients sometimes prefer to seek counselling closer to home.
2) Potential clients should be evaluated neurologically, neuropsychologically and psychiatrically.
3) Relatives at risk or symptomatic who are donating a DNA sample for a client to be tested should be evaluated neurologically as well. A diagnosis should not be accepted on the basis of hearsay evidence, even from a family member. Corroboration should be sought from the diagnosing physician and a re-evaluation should be arranged if there is any doubt. If persons at risk cannot or will not be examined, their risk should be assigned very conservatively in the linkage analysis. The disease should be confirmed in at least one relative by autopsy diagnosis or by very reliable neurological examination.
4) Clients found to have significant psychiatric disorders, particularly a history of suicide or severe depression, or those undergoing stressful life circumstances causing emotional upheaval, such as divorce or a death in the family, are not suitable testing candidates.
5) Diagnostic information must always be given in a face- to-face session, never over the telephone. Even if the outcome is genetically uninformative, clients need an opportunity to discuss what this information may mean.
6) Most programs require or strongly urge that clients be accompanied by a companion to at least one counselling session and at the disclosure session.
7) Long-term follow-up is essential, particularly for those who test positive for the gene. As the time draws near when symptoms are likely to appear, clients need to know that they have a relationship with a supportive therapeutic individual or group.
8) Some programs require that a client contact a psychotherapist prior to receiving diagnostic information. Other programs provide the therapists. These therapists can continue to see clients, particularly after a positive diagnosis.
9) All DNA determinations must be carried out independently at least twice. If contradictions appear, new DNA samples are collected. Some centres collect two independent blood samples. If blood has been donated from relatives for research purposes these samples must be re-collected unless explicit permission is given for them to be used in diagnostic testing. Even then it is best to collect new samples on crucial individuals.
10) A genetic linkage computer analysis of haplotypes generated must always be conducted. Diagnostic information must never be given on the basis of a visual analysis of the gels alone.
11) If siblings of a client need to be analyzed to determine phase or to reconstruct the haplotype of a deceased parent, the identities of these siblings should be confidential and data analyzed anonymously. This prevents those providing counselling from inadvertently receiving unwanted and inappropriate information.
12) Testing should be available only to persons aged 18 years or older who can give informed consent. One potential complication of this guideline may occur if parents have a non-disclosing prenatal test and choose to maintain a pregnancy in which the foetus is found to have a 50% risk. If the at-risk parent develops Huntington's disease, the child is de facto diagnosed. Another ethical quandary may occur when couples who wish to adopt a child at risk insist on testing as a condition of adoption.
13) All testing must be totally voluntary and the results remain totally confidential, even to other family members.

* Adapted from: Genetics, Ethics And Human Values. Human Genome Mapping, Genetic Screening And GeneTherapy. Proceedings of the XXIVth CIOMS Round Table Conference. Edited by Z. Bankowski and A.M. Capron. Tokyo and Inuyama City, Japan, 22-27 July 1990.

The presymptomatic direct DNA-test was introduced in 1997, after extensive debate and evaluation of the results of psychological research of linkage testing. The original protocol used for presymptomatic testing in Huntington's disease (Table 8), used since 1988, has been accompanied by psychological studies in many of the countries in which it was introduced [76,77,78,79,80,81,82,83]. Recommendations concerning the use of a presymptomatic test for the detection of Huntington's disease (HD) were drawn up by a committee consisting of representatives of the International Huntington Association (IHA) and the World Federation of Neurology (WFN) Research Group on Huntington's Chorea.

The establishment of a committee with the specific task of preparing such guidelines was agreed upon at the WFN and IHA conferences in Lille, France, in September 1985. The first recommendations were adopted by each of the organizations at their respective meetings in Vancouver, BC, Canada in1989, and published [84]. Revision of these guidelines was necessary in view of the report, published in March 1993, of the detection of the gene defect [85].

Worldwide use of this predictive genetic counselling protocol was shown not to lead to catastrophic events (suicide, suicide attempts or psychiatric hospitalization) more often than in the general population [86].

The 'Huntington protocol' was used as paradigm for the development of guidelines regarding presymptomatic or predictive testing in other (incurable) neurologic diseases and in oncogenetics. Counselling is internationally regarded essential, before any genetic testing is carried out [87]. The American Society of Clinical Oncology published general guidelines for genetic testing in cancer susceptibility in 1996 and 2003 (e.g. hereditary breast/ovary and colonic cancer), derived from guidelines for genetic testing in Huntington's disease (Table 9) [88,89]. Because heritable forms of cancer are more or less preventable, these guidelines can serve as a model for guidelines in cardiogenetics. To date, the data on psychological outcomes after genetic counselling and testing in breast cancer are comforting. However, few studies used a randomised trial design, limiting the strength of the conclusions. Follow-up to date has

Table 9. Basic elements of informed consent for germline DNA-testing for cancer susceptibility according to the American Society of Clinical Oncology*

1. Information of the specific test being performed
2. Implications of a positive and negative test result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic testing
5. Risk for passing a mutation to children
6. Technical accuracy of the test
7. Risk of psychological distress
8. Risk of insurance or employer discrimination
9. Confidentiality issues
10. Options and limitations of medical surveillance and screening following testing
11. Fees involved in testing and counselling

* Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility. J Clin Oncol 1996; 14: 1730-6.

been short, and we know little about the long-term impact of testing on patient behaviours, perceptions and psychological state [90].

Biesecker and Marteau envisage an expansion of professional roles and expertise for many health care providers and highlight the need for counselling practices to become more evidence based. Although they support an evidentiary-based approach for implementing genetic testing into practice, they expect that genetic advance is unlikely to occur in an orderly fashion within countries, much less among different countries and health care systems [91].

-Organisation of genetic counselling in the Netherlands

Eight clinical genetic centres, all attached to university hospitals, deliver clinical genetic care in the Netherlands. The provision of DNA diagnostics is always connected with provision of genetic counselling. For clinical genetic testing and genetic counselling, permission from the Dutch Minister of Health is still required. In 1983 a ministerial decree based on Section 18 of the Hospital Provisions Act came into force, limiting specialised care (including genetic counselling and testing) to those with a permit from the minister of Health, Welfare and Sport. In 1997 all top clinical activities were made subject to section 2 of the Specific Medical Procedures Act. Only clinical geneticists employed in clinical genetic (academic) medical centres may provide complex genetic counselling in the scope of predictive molecular testing, activities defined as specialised care. In 2003 a total of 15,916 new counselling sessions were started in the Netherlands. Their annual increase is approximately 10% [92]. Clinical geneticists have in 2000 been asked to develop guidelines for a number of clinical situations, which include predictive genetic testing and genetic testing in children. Moreover both medical and laboratory professional organisations have already initiated a number of self-regulatory measures [93,94]. Ten years ago 'genetic consulents' joined in. 'Genetic consulents' are registered nurses or paramedics who have subsequently graduated from a two year in-service training in genetic counselling and whose registration and accreditation is taken care for by the Dutch Society of Clinical Genetics (VKGN). Their professional skills can be compared with genetic counsellors and genetic nurses in other countries. In the near future a Master's-program for Dutch genetic counsellors will be launched, in collaboration with the VKGN. Currently 29 'genetic consulents' have been registrated and another 16 are in training. Sufficient facilities for DNA testing, genetic counselling and monitoring are available. Counselling as well as DNA testing are reimbursed (fee for service remuneration).

In case of cardiogenetics, in most centres regular joint outpatient clinics are held in presence of a clinical geneticist and a cardiologist at the same session, with involvement of psychosocial workers where needed. In 2003 989 new counselling sessions were devoted to cardiogenetic diseases (6,2%). In our centre (AMC) the cardiogenetic sessions made up 25% of the total production in 2003 and 2004. Cardiologists are currently not allowed to request DNA-diagnostics in their patients [95]. Given the still highly specialised character of diagnosing and DNA-testing in cardiogenetics, the role of general practitioners in cardiogenetic care is currently highly limited.

-Reasons for attending cardiovascular counselling

In genetic counselling two situations have to be distinguished. First: affected individuals (or parents of an affected child) coming for a diagnosis to be made or confirmed (by clinical and/or dysmorphologic examination and/or the use of genetic techniques) and/or for counselling to discuss reproductive aspects of the disorder. Second: healthy asymptomatic people who want to be informed about their genetic status and their risk of developing a specific disorder during their life, often after the identification of such a disorder in a relative. The latter is referred to as presymptomatic or predictive counselling. As stated, in recent years genetic counsellors have obtained a lot of experience in presymptomatic counselling and testing from dealing with (untreatable) neurodegenerative disorders and heritable forms of cancer.

Visitors with the request for genetic counselling at the cardiogenetics outpatient clinic most commonly are:

a) Individuals affected with a known (or suspected) cardiovascular disorder who want to know more about the clinical and heritable aspects of their disease, and apply for genetic testing
b) Patients with cardiovascular disease who want to be informed about the risk of transmitting this disease to offspring, about ways to avoid or diminish this risk and (seldom) to be informed about options for prenatal diagnosis
c) Parents of children with cardiovascular disease who want to know the recurrence risk in a next pregnancy
d) Relatives of affected patients who want to know if they and their children are at risk for the same disorder (e.g. cascade screening)
e) Counsellees with multiple cases of heart disease in their families (congenital and/or structural and/or with onset later in life) who want to know if this condition increases the risk of such a disease for themselves and their children
f) Counsellees with one or more cases of sudden cardiac death in their family who want to know if they (and their children) are at risk

2. Genetic Testing

-Modalities of genetic testing in general

Genetic testing is the use of specific tests for the analysis of a gene, its product or function, in individuals who are at increased risk of having a genetic disorder because of their family history of own symptoms [96]. Genetic testing can be established for diagnosing a specific disease in a patient or to determine carrier status to detect susceptibility or predisposition to this disease (in healthy people predicting a late-onset disease like HCM). Genetic testing not only refers to investigations of DNA or chromosomes but can also refer to the analysis of proteins, certain metabolites or even of the ECG (e.g. in LQTS) or the echocardiogram (in HCM), assuming that these investigations may reveal a genetic predisposition. Genetic testing can be performed in the context of treatment, management or implementation of preventive measures in disease to modify the severity of the disorder. It can also be used to supply information on the risks for offspring or to enable prenatal diagnosis. In primary arrhythmias and cardiomyopathies prenatal diagnosis is currently seldom requested, most

probably because preventive treatment can be offered. Predictive testing should always be surrounded by pre-test and post-test counselling, as described in the guidelines on testing for Huntington's disease and cancer susceptibility, independent by whom or in which way the genetic information is obtained.

a. Diagnostic testing

The term diagnostic genetic (molecular) testing is being used when a person or foetus has or is suspected of having a particular disorder on clinical or genetic grounds and molecular techniques (DNA-testing) are being used for making, confirming or refining of the diagnosis. An example is the use of genetic investigations in a person with recurrent syncope's and a prolonged QT-interval. By screening the eligible genes and finding a mutation the diagnosis can be confirmed, the type of LQTS, and thereby the most effective treatment ,becomes clear and family studies are facilitated.

When healthy individuals (including the foetus in prenatal testing) undergo genetic (molecular) testing for a disease running in their family, this is a *predictive or presymptomatic genetic test*. The term *presymptomatic* is generally reserved for situations where an abnormal test result almost invariably implies the development of the disorder later in life. An example is Huntington's disease; when the characteristic (familiar) lengthened repeat in the Huntington gene is detected on one allele in a young person, it is almost certain that he or she will get all neurological symptoms of this devastating disease in the distant future. With the results of *predictive* testing, the risk of developing (the symptoms of) a disorder is generally can be specified. DNA-testing in a healthy person closely related to a LQTS patient with a proven mutation can be considered a predictive test; the result of the test can reduce the risk of dying suddenly at young age to, nearly, zero (not having the familiar mutation) or considerably enlarge the risk in carriers. However, it is impossible to predict if this carrier will ever get symptoms, because life-long penetrance is reduced. Besides, it is not possible to predict the severity or age of onset of the disease. The same accounts for most other primary arrhythmias and cardiomyopathies.

In general, predictive molecular testing is only possible in families where the causal mutation in the index patient has already been identified. In other cases predictive testing in cardiogenetics is possible by cardiologic screening. Not finding clinical signs of the disease does not imply that the mutation is absent however, due to the reduced (and age-dependent) penetrance in these disorders. The justification of predictive testing in children has always been a point of debate. As with any other medical intervention, when children do not have the capacity to provide voluntary, informed consent, the decisive consideration in genetic testing in children should be the welfare of the child [97]. In cardiogenetics symptoms can start at young age (in LQTS and CPVT in particular) and effective prophylaxis is possible, so testing in children for these diseases seems justified.

b. Genetic (population) screening

Genetic population screening differs from genetic testing in individuals or families. Here a certain population is actively invited by medical or governmental organisations for testing to

identify persons at risk, independent of family history or manifestation of symptoms. Primary goals of genetic screening are the timely prevention of deleterious effects of the disorder by prophylactic treatment or lifestyle rules (e.g. dietary measures in phenylketonuria, medication and dietary measures in familial hypercholesterolemia). Prevention of sudden death at young age could be a goal of genetic population screening as well. An example is preparticipation testing in competition- or top sports. DNA-testing, but also cardiologic screening could be used to achieve this goal. The feasibility of population screening regarding this issue is discussed in Chapter 4. Principles, techniques, practices and policies of population screening programs were reviewed by Godard et al, based on a ESHG-workshop with experts from 15 European countries in 1999 [98]. They conclude that 'the general impression on the future of genetic screening is that one wants to 'proceed with caution', with more active impetus from the side of patients' organizations and more reluctance from the policy-makers.

c. Cascade screening

Cascade screening is an intermediate form between individual genetic testing and population screening: In families with genetic disorders in which prevention is somehow possible and in which a causal mutation is identified, all first degree (and second degree, in case of deceased first degree relatives) are actively invited, by relatives or by medical workers, to undergo predictive testing. Cascade screening has proven to be feasible in families with familial hypercholesterolemia [99,100,101]. The feasibility of cascade screening in primary arrhythmias and cardiomyopathies is discussed in Chapter 4.

D. Scope and outline of this thesis

Many questions regarding the optimal organisation and design of clinical genetic care for patients and families with diseases predisposing to sudden death still need to be addressed. Research on these topics has scarcely been performed yet, also due to the fact that diagnostic (commercial) molecular testing in primary arrhythmias and cardiomyopathies has only recently become possible internationally. The initiation of the cardiogenetic outpatient clinic in our centre(s) was initially driven by cardiologic research interest, aimed at the molecular background of these disorders and eventually at the (possible) molecular background of multifactorial, common, diseases associated with cardiac arrhythmias. From a clinical geneticists point of view, the initiation of this outpatient clinic offered an unique chance to 'create' a new category of patient care in genetics, closely resembling, but also different in many aspects from genetic counselling and molecular (predictive) testing in Huntington's (and other neurological) disease and in oncogenetics. We therefore translated some of the questions regarding the organisation and design of care into research questions and attempted to answer them, while continuing and expanding the work at our cardiogenetic outpatient clinic.

In **Part I** of this thesis research regarding the (future) multidisciplinary organisation of care is described. In ***chapter 2*** the current (year 2000) genetic knowledge and counselling skills of Dutch cardiologist are investigated and suggestions are made for improvement. In ***chapter 3***

the preferences of Dutch cardiologists and clinical geneticists for the future organisation of genetic care in hypertrophic cardiomyopathy (as a prevalent cardiogenetic model disease) are presented.

In **Part II** various aspects of genetic counselling and screening in cardiogenetics are investigated and described. *Chapter 4* deals with family and population strategies for screening and counselling in inherited cardiac arrhythmias. *Chapter 5* consists of a paper on the societal aspects of genomics, regarding heritable diseases associated with sudden death. In *chapter 6* research on the client's perspective is presented. In particular agenda's (questions and reasons for attending) and backgrounds of counsellees at the cardiogenetic clinic compared to those of counsellees attending the clinical genetics department for other diseases are analysed . *Chapters 7 and 8* describe the psychological consequences of predictive genetic testing in LQTS.

Part III *(chapter 9)* finally reports on the use of genotype-phenotype correlations to enhance efficiency in molecular genetic testing in LQTS.

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