ICPerMed Best Practice in Personalised Medicine Award 2018. Berlin, 21 November 2018.

NAGEN
PROYECTO GENOMA 1000 NAVARRA

Navarra 1,000 **Gen**omes Project (**NAGEN 1000**): *An example of a Project for Regional Implementation of Personalised Genomic Medicine in Healthcare*

Project with a nomination by ICPERMED AWARD 2018 "Best Practice in Personalised Medicine

"Best Practice in Personalised Medicine" Award 2018

Angel Alonso
NAGEN Project Director.

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PROYECTO GENOMA 1000 NAVARRA

Nafarroako Gobernua
Garapen Ekonomikorako Departamentua

Gobierno de Navarra
Departamento de Desarrollo Económico

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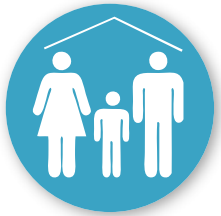
Pyramide Asesores

Context



Personalised Genomic Medicine applications:

- Diagnosis of diseases of genetic cause .
  - Prediction, prevention
  - Reproductive options
- Characterization of genetic variants related to personal risk.
- Identification carriers of serious genetic diseases.
- Identification of genetic variants responsible for pharmacological response.
- Stratification of patients for care management
- Promote research and innovation.
- Improve the quality of health care, better quality of life and save costs.

Aims NAGEN 1000

"Implementation of the use of information derived from WGS as a clinical tool for the development of personalised medicine in Navarre Public Health Service (SNS)"

- Translational research, innovation & genomics industry development

Secuencing 1,000 whole genomes from SNS patients with rare diseases.

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NAVARRE HEALTH

Methodology

▶ Implementation Science Approach

> "It takes 17 years on average to convert the results of the research to benefit the patient"
David Chambers, director Implementation science National Cancer Institute.

> "It is the method to promote the integration of research findings in health care" **(NIH, 2016).**

> Tools: Pilot projects and Identification of Barriers.

Results: Barriers

Local barriers for Genomic Medicine Implementation in Navarra (NAGEN 1000 project):

Codependent Tech

- No high throughput genome sequencing facility.
- No bioinformatics platforms/staff.
- No preclinical evidence of the effectiveness of interventions.

ICT

- No adequate infrastructures designed to genomic data storage.
- Absence of supercomputing for genomic data processing.
- EHR inadequate to connect with genomics.

ELSI

- Concerns over consent and privacy of genomic data.
- No adequate legal framework.
- Ownership of genomic information for research and marketing purposes.

Education & Awareness

- Resistance to the change of routine medical practices.
- Inadequate Health professionals profiles
- Public unawareness

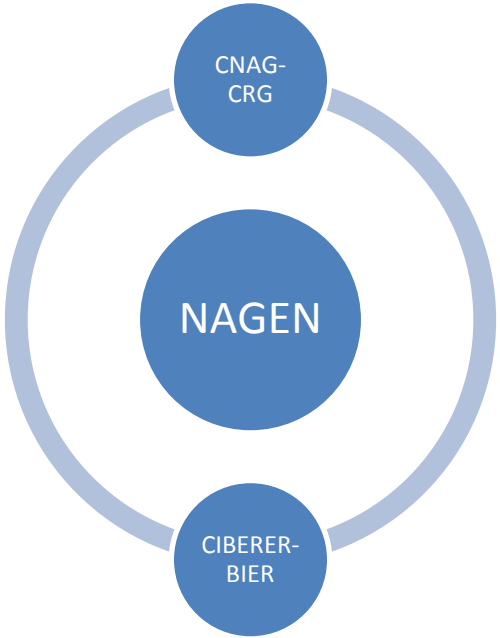
Sustainability

- Misaligned financial incentives
- Need to align with the future burden of disease and health
- No national strategy on PM

Results: Key Actions for this implementation

> **Optimized use of pre-existing public infrastructures**

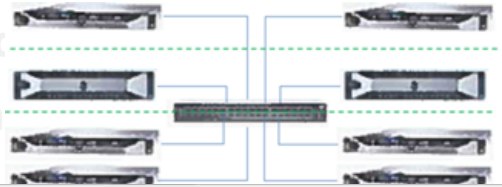
- **CNAG-CRG** is a non-profit SEQUENCING PLATFORM funded by the Spanish Ministry of Science, Innovation and Universities and the Catalan Government .
- **CIBERER-BIER**, is a transversal BIOINFORMATICS PLATFORM funded by the Spanish Ministry of Science, Innovation and Universities and the Andalucia Government.

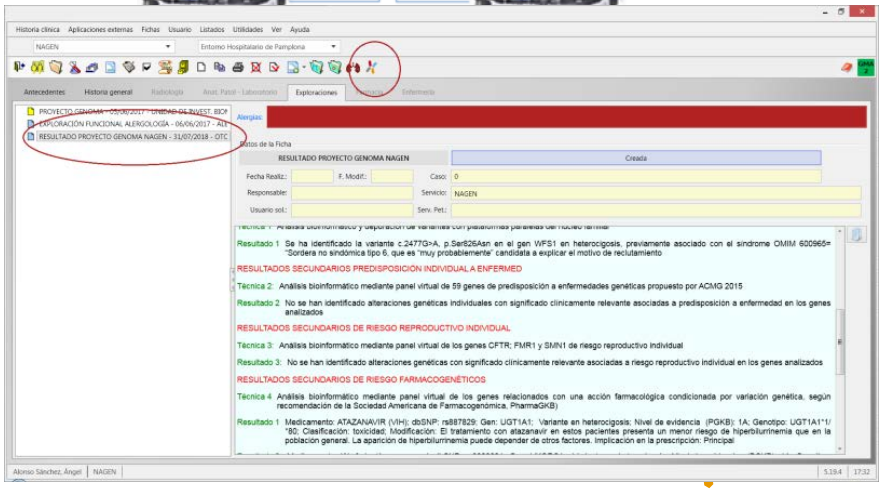


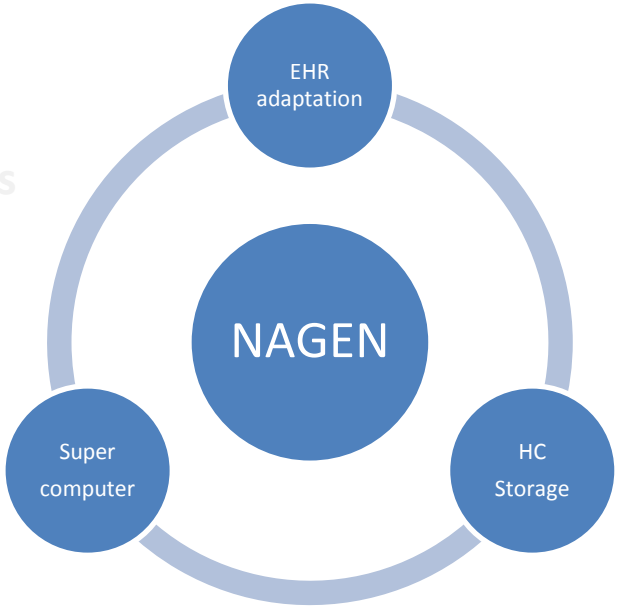
Results: Key Actions for this implementation

> > ICT

- 4 calculating nodes (IBM POWER 9 superprocessor).
- Infiniband transmision 100Gb/s







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NAVARRE HEALTH

Results: Key Actions for this implementation

> Education and training

> Dissemination

NAGEN monographic symposiumS (CHN, NB)	2
Hospital Clinical sessions CHN	1
Interhospitalary presentations (Comarcal, Primary)	3
Services clinical sessions	9
National Scientific Communications (CIBER,CNAG)	3
International Scientific Communications (British Society Genetics)	1
National Strategic Communications (Spanish Senate, Roche Institute, Sapanish Hospital CEOs meeting)	2
International Strategicc Communications (DG Sante, EC)	1
International Concerted actions(CEIN, Pirepred)	2
General Public information (National Science Week, RD Patient association)	2
Press conferences and media difusion (news papers, radio, TV)	1
Website	1
IC PerMed Best Practice in Personalised Medicine Award 2018	1

https://www.nagen1000navarra.es/:

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NAVARRABIOMED CENTRO DE INVESTIGACIÓN BIOMÉDICA

NAGEN PROYECTO GENOMA 1000 NAVARRA

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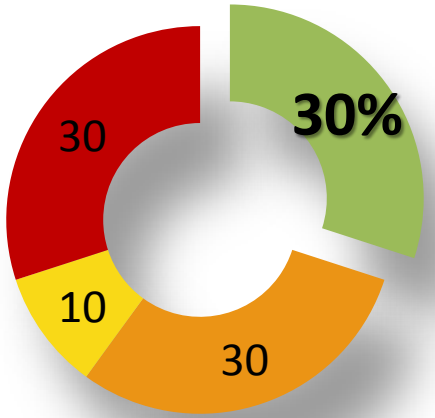
NAVARRE HEALTH

Results: Key Actions for this implementation

> Preclinical Evidence

Ref	Referal Code	Gen	Tránscrit	Heteroxygosity	Mutation HGVS	OMIM	ClinVar
E0036.01	Hearing Loss	WFS1	ENST00000226760	Heterozygous	c.2477G>A p.Ser826Asn	600965 DEAFNESS, AUTOSOMAL DOMINANT 6; DFNA6.	
E0001.01	Balanced translocations	FAM227B	ENST00000299338	Heterozygous	46,XY,inv(15)(q21q24)		
E0009.01	Intelectual disability	KMT2A	ENSG00000118058	Heterozygous	c.654delA p.Ile218fs	605130. WIEDEMANN-STEINER SYNDROME	
E0009.01	Intelectual disability	KMT2A	ENSG00000118058	Heterozygous	c.656A>G p.Glu219Gly	605130. WIEDEMANN-STEINER SYNDROME	
E0015.01	Neurofibromatosis 1	SPRED1	ENST00000299084	Heterozygous	c.46C>T p.Arg16*	611431 LEGIUS SYNDROME	372718
E0017.01	Intelectual disability	PPM1D	ENST00000305921	Heterozygous	c.1274_1277dupGAGG, p.Asp425fs	617450 INTELLECTUAL DEVELOPMENTAL DISORDER WITH GASTROINTESTINAL DIFFICULTIES AND HIGH PAIN THRESHOLD; IDDGIP	
E0018.01	Hereditary Ataxia	LMNB1	ENST00000261366	Heterozygous	c.626A>G p.Lys209Arg	169500 LEUKODYSTROPHY, DEMYELINATING, ADULT-ONSET, AUTOSOMAL DOMINANT; ADLD	
E0024.01	Balanced translocations	FAAH2	ENST00000374900	Heterozygous	46,X,t(X;10)(p11;q26)	300654. FATTY ACID AMIDE HYDROLASE 2; FAAH2	
E0024.01	Balanced translocations	NHLRC2	ENST00000369301	Heterozygous	46,X,t(X;10)(p11;q26)		
E0026.01	Intelectual disability	WDR45	ENST00000356463	Heterozygous	c.971delT p.Val324fs	300894 NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 5; NBIA5.	
E0029.01	Familial Pulmonary Fibrosis	TERT	ENST00000310581	Heterozygous	c.1403G>C p.Cys468Ser	614742. PULMONARY FIBROSIS AND/OR BONE MARROW FAILURE, TELOMERE-RELATED, 1; PFBMFT1	
E0001.01	Balanced translocations	SIN3A	ENST00000394947	Heterozygous	46,XY,inv(15)(q21q24)		
E0035.01	Undiagnosed metabolic diseases	ALDOB	ENST00000374855	Homozygous	c.448G>C p.Ala150Pro	229600 FRUCTOSE INTOLERANCE, HEREDITARY.	464
E0097.01	Kidney Proteinuria	INF2	ENST00000330634	Heterozygous	c.641G>A p.Arg214His	613237 FOCAL SEGMENTAL GLOMERULOSCLEROSIS 5; FSGS5	1053
E0040.01	Familial Breast Cancer	BRCA1	ENST00000357654	Heterozygous	c.5123C>A p.Ala1708Glu	604370, BREAST-OVARIAN CANCER, FAMILIAL 1 113705, BRCA1	55407
E0059.01	Artrogriposis	CRLF1	ENST00000392386	Heterozygous	c.713dupC p.Pro239Alafs	272430 CRISPONI/COLD-INDUCED SWEATING SYNDROME 1; CISS1	216913
E0059.01	Artrogriposis	CRLF1	ENST00000392386	Heterozygous	c.803T>C p.Phe268Ser	272430 CRISPONI/COLD-INDUCED SWEATING SYNDROME 1; CISS1	
E0059.01	Artrogriposis	CRLF1	ENST00000392386	Heterozygous	c.1018C>T p.Arg340Cys	272430 CRISPONI/COLD-INDUCED SWEATING SYNDROME 1; CISS1	
E0066.01	Noonan syndrome	PTPN11	ENST00000351677	Heterozygous	c.417G>C p.Glu139Asp	163950 NOONAN SYNDROME 1; NS1 and 156250 METACHONDROMATOSIS; METCDS	40513
E0077.01	Charcot-Marie-Tooth disease	SBF2	ENST00000256190	Homozygous	c.1281T>A p.Cys427Ter	604563 CHARCOT-MARIE-TOOTH DISEASE, TYPE 4B2; CMT4B2	
E0079.01	Charcot-Marie-Tooth disease	RAB7A	ENST00000265062	Heterozygous	c.484G>A p.Val162Met	602298. RAS-ASSOCIATED PROTEIN RAB7; 602298. RAS-ASSOCIATED PROTEIN RAB7; RAB7A, Approved Gene Symbol: RAB7A	7346
E0080.01	Charcot-Marie-Tooth disease	MPZ	ENST00000533357	Heterozygous	c.148T>C p.Cys50Arg	159440. CHARCOT-MARIE-TOOTH DISEASE CMT1B, CMT2I, CMT2J, DEJERINE-SOTTAS, CHN, ROUSSY-LEVY DYSTASIA	
E0086.01	Epiléptic Encephalopathy	SCN1A	ENST00000303395	Heterozygous	c.2585G>A p.Arg862Gln	607208 EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 6; EIEE6	
E0089.01	Familial hematuria	COL4A4	ENST00000396625	Heterozygous	c.735+2T>C	120131; COL4A4; Alport syndrome.	
E0093.01	Complex Parkinsonism	LRRK2	ENST00000298910	Heterozygous	c.4321C>G p.Arg1441Gly	609007; LRRK2, PARK8; Parkinson disease 8	1936
E0030.01	IUGR y IGF Abnormalities	IGF1R	ENST00000268035	Heterozygous	c.307C>T p.Leu103Phe	OMIM:270450 INSULIN-LIKE GROWTH FACTOR I, RESISTANCE TO, DUE TO INCREASED BINDING PROTEIN	



- Diagnosis achieved
- Strong candidate diagnosis
- Mild candidate diagnosis
- No diagnosis

Results: Key Actions for this implementation

> Preclinical Evidence

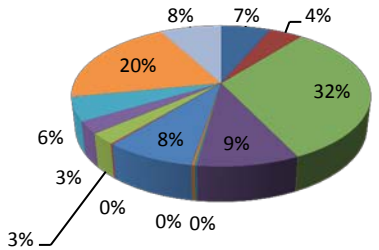
Secondary Results			
Risk	Consent	Number of patients	**% of cases**
Disease risk	211	11	**5,2%**
Reproductive Risk	221	12	**5,4%**
Pharmacogenomics	231	231	**100%**

Disease risk results			
Gen	Mutación	Enfermedad	Nº pacientes
APC	c.3920T>A, p.Ile1307Lys	175100. FAMILIAL ADENOMATOUS POLYPOSIS 1	2
ATP7B	c.1934T>G, p.Met645Arg	277900. WILSON DISEASE	10
BRCA2	c.658_659delGT p.Val220IlefsTer4	114480.BREAST CANCER	1
MUTYH	c.1187G>A p.Gly396Asp	608456. FAMILIAL ADENOMATOUS POLYPOSIS 2; FAP2	5
MUTYH	c.536A>G, p.Tyr179Cys	608456. FAMILIAL ADENOMATOUS POLYPOSIS 2; FAP2	2

PHARMGKB

Pharmacogenetic variants distribution

- CYP2C19 Clopidogrel, Citalopram/Escitalopram; Amitriptyline;Voriconazol
- CYP2C9 Fenitoína
- CYP2D6 Diversos fármacos: amitriptyline/ antidepressants/ clomipramine/ desipramine…
- CYP3A5 Tacrolimus
- DPYD Capecitabina, 5-FU, Tegafur
- G6PD Rasburicasa, Cloroquina, Dapsona, Clorpropamida.
- IFNL3 Peg-interferón y ribavirina
- NUDT15 Tiopurinas



Conclusions

- NAGEN 1000 as a model for Personalised genomic medicine implementation in the Public Health Service:
  - Multidisciplinary participation of professionals and patients.
  - Optimizes the use of resources and the development of new ones.
  - Provides training, specialization.
  - Produces scientific findings that increase knowledge.
  - Opens the integration and analysis of big data health and promotes innovative ICT solutions.
  - Encourages the adaptation of ethical legal principles to new technologies.
  - Facilitates cooperation between sectors.
  - Evidences the need for national and international strategies.
  - Enables the application of Genomic Medicine and prepares de basis of Personalised Medicine.

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NAGEN PROYECTO GENOMA 1000 NAVARRA

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