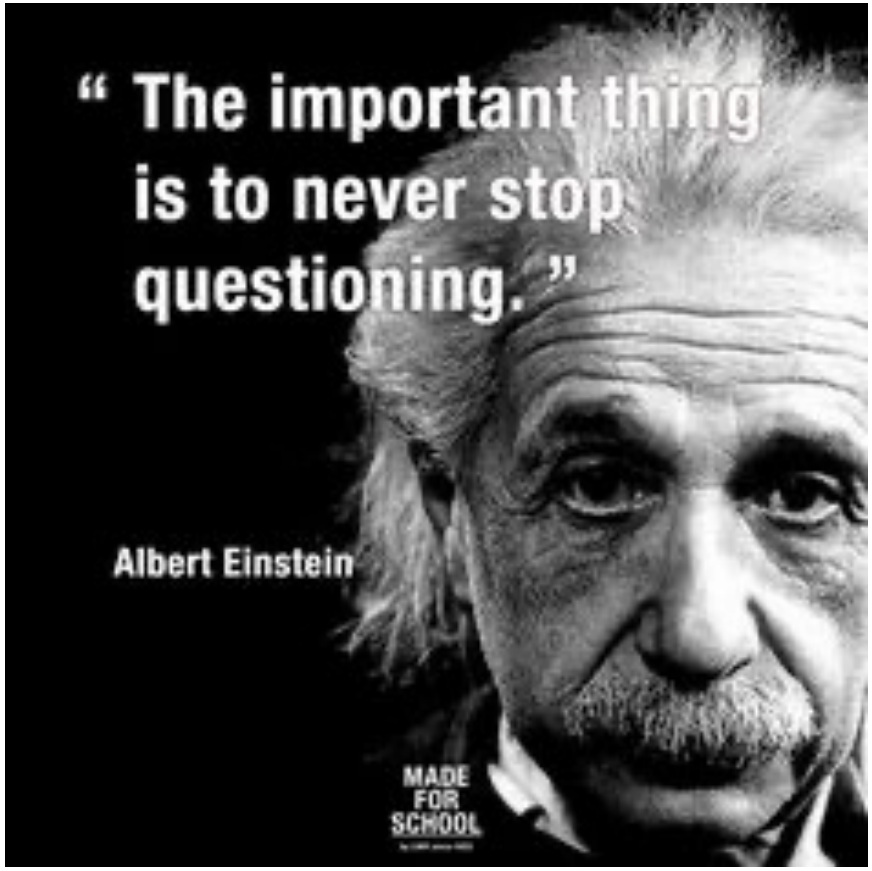

“ The important thing is to never stop questioning. ”
Albert Einstein
MADE FOR SCHOOL

Which are the trial phases

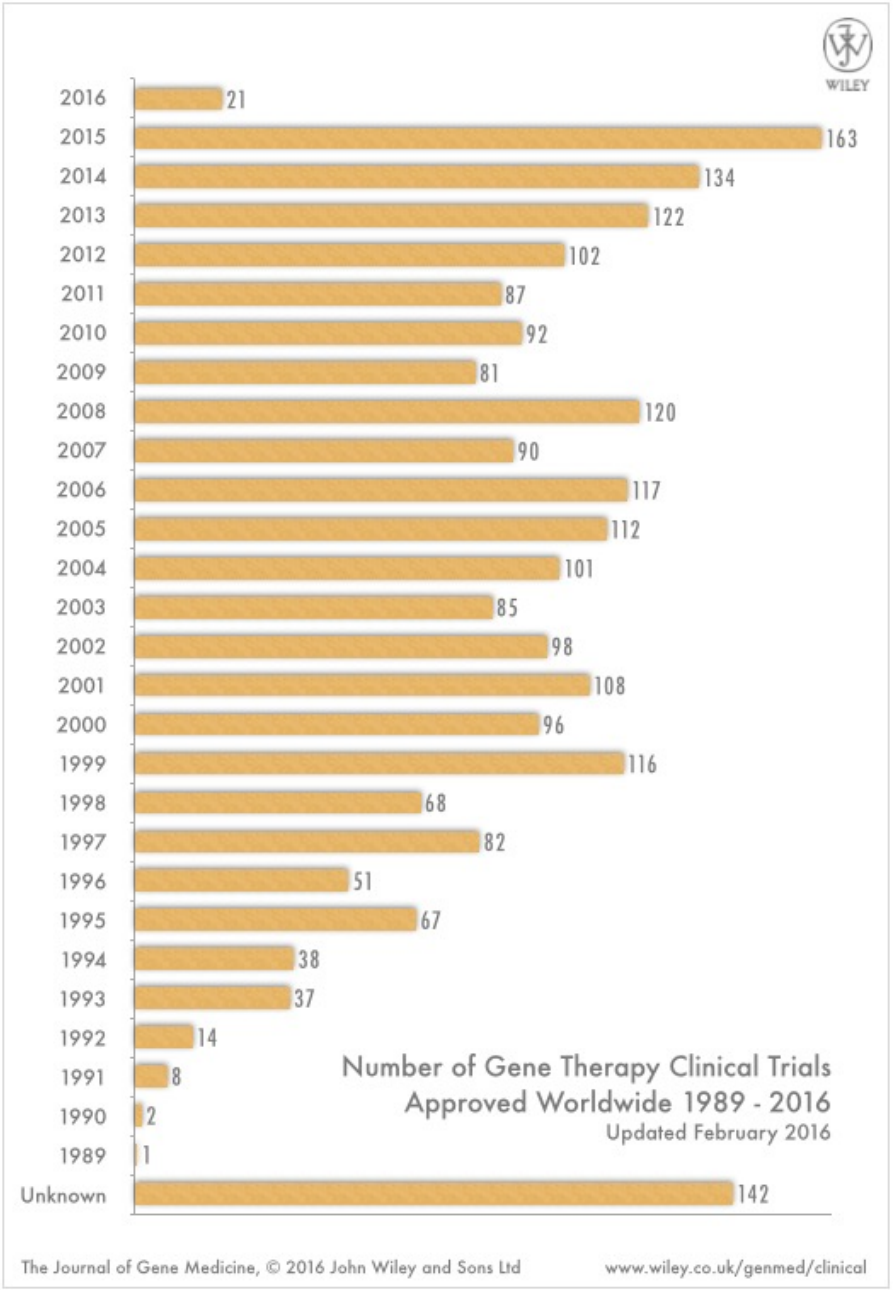
- Phase I: small number of patients (20-80) fpr pharmacovigilance, pharmacokinetics, pharmacodynamics

- Phase II: performed on larger groups (20-300) and designed to assess clinical efficacy of the therapy; as well as to continue Phase I assessments

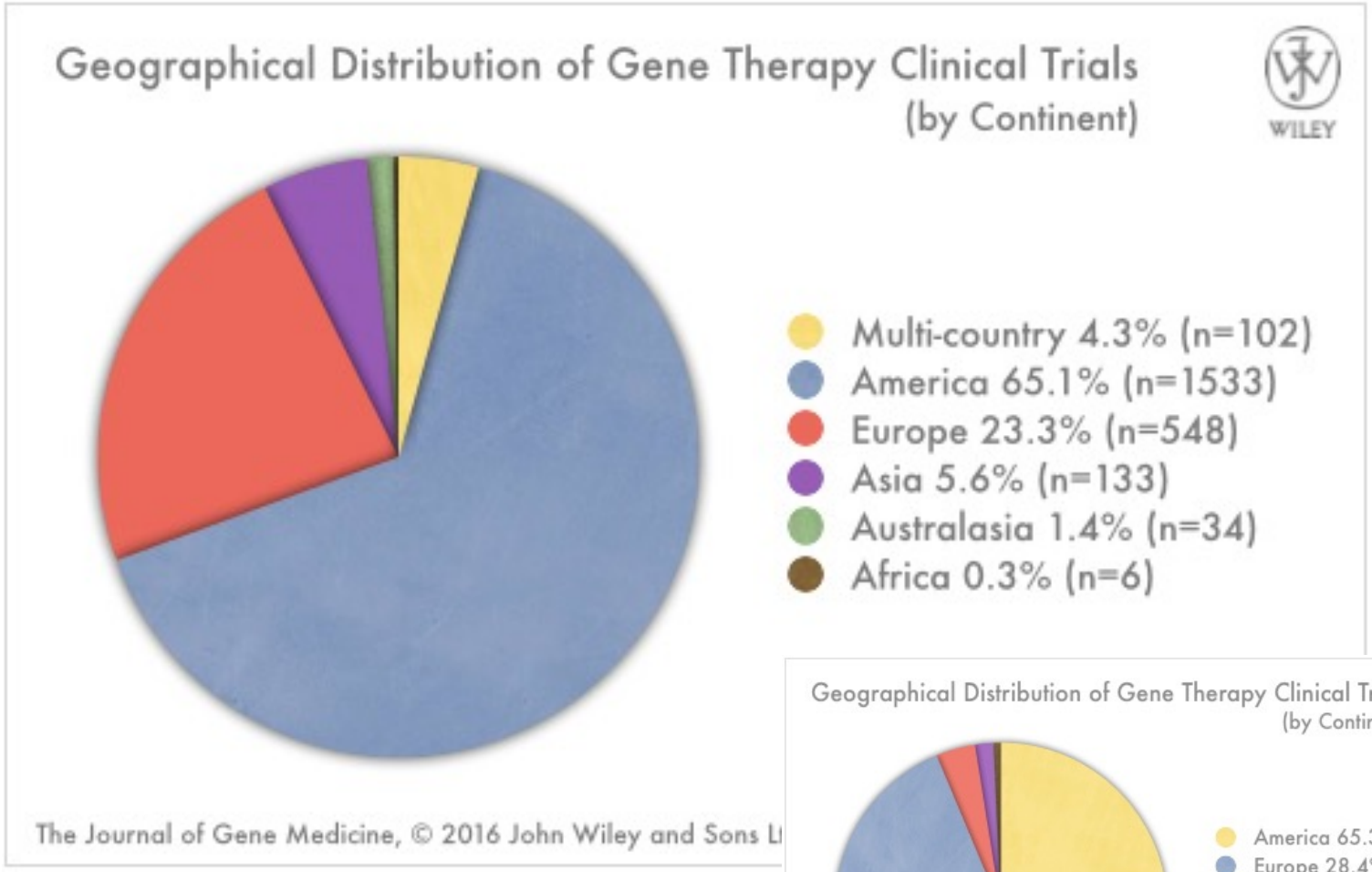
- Phase III: randomized controlled trials on large patient groups (300-3000 or more depending upon the condition) and are aimed at being the definitive assessment of the efficacy of the new therapy, in comparison with current 'Gold Standard' treatment.

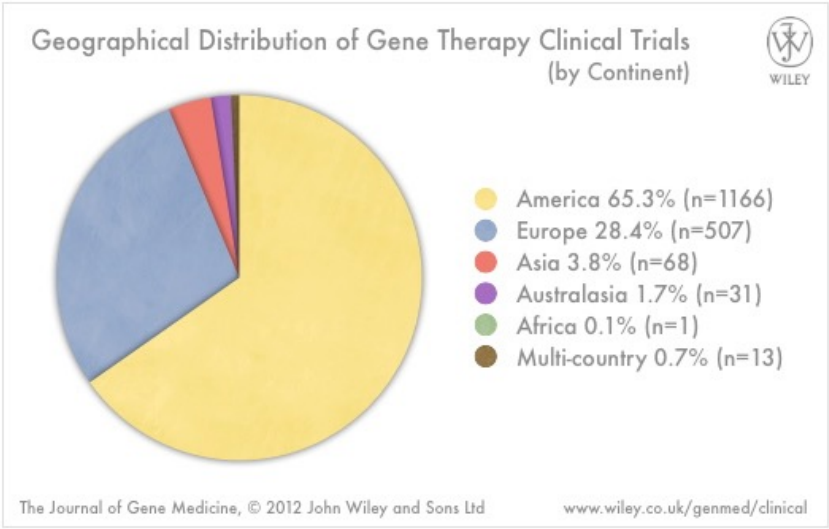
- Phase IV: involve the post-launch safety surveillance and ongoing technical support of a drug.

Clinical trials – 2016 update

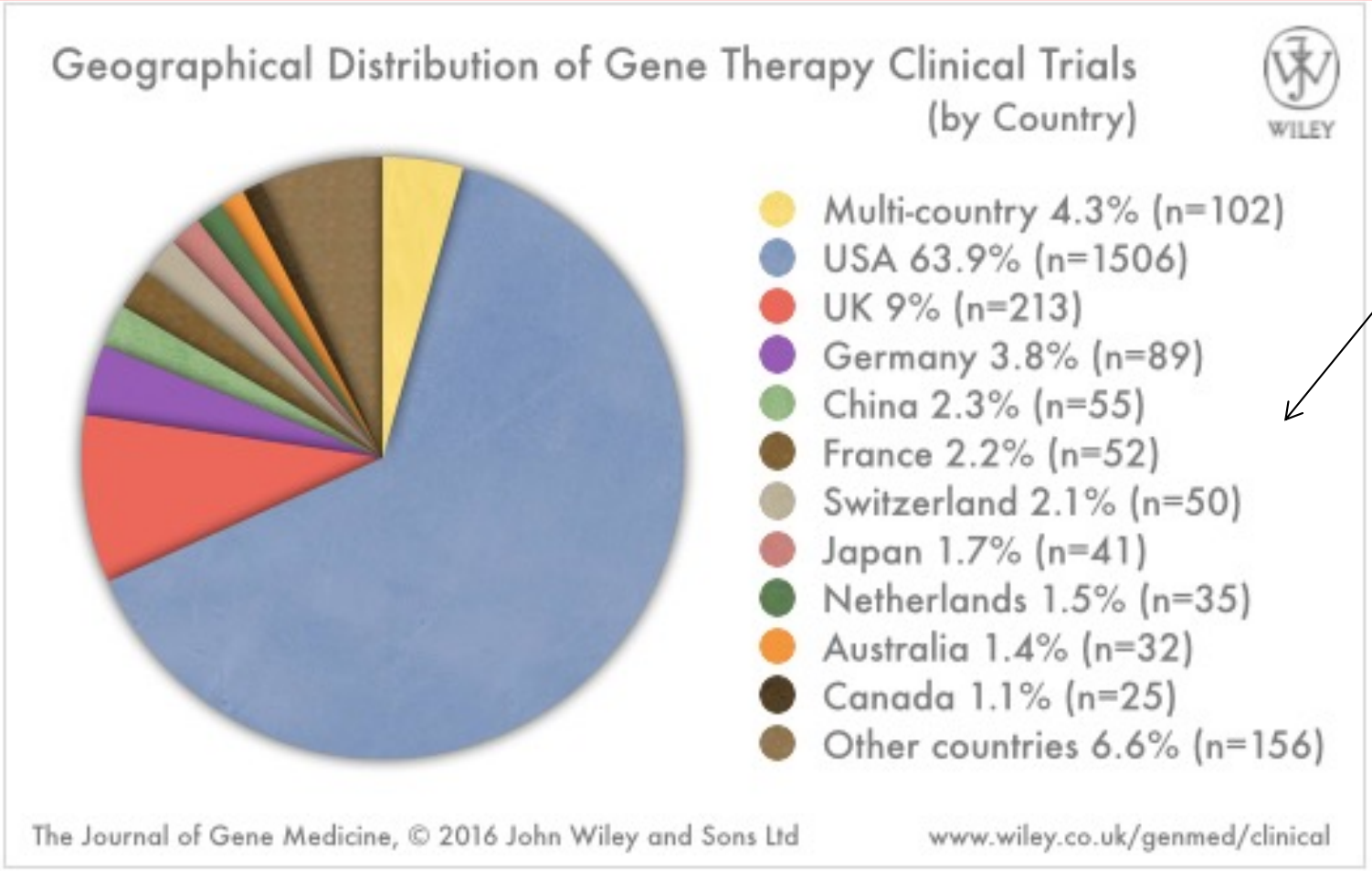


Trials/continent





Trials/country



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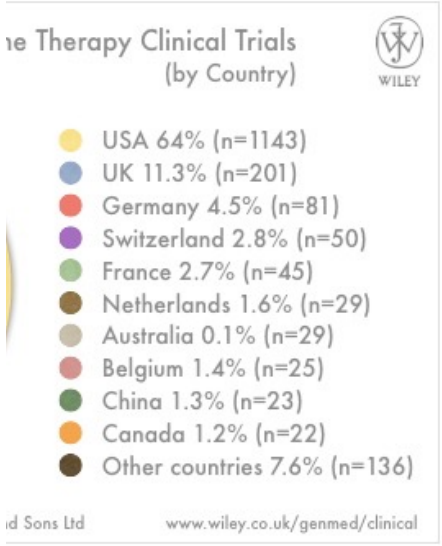
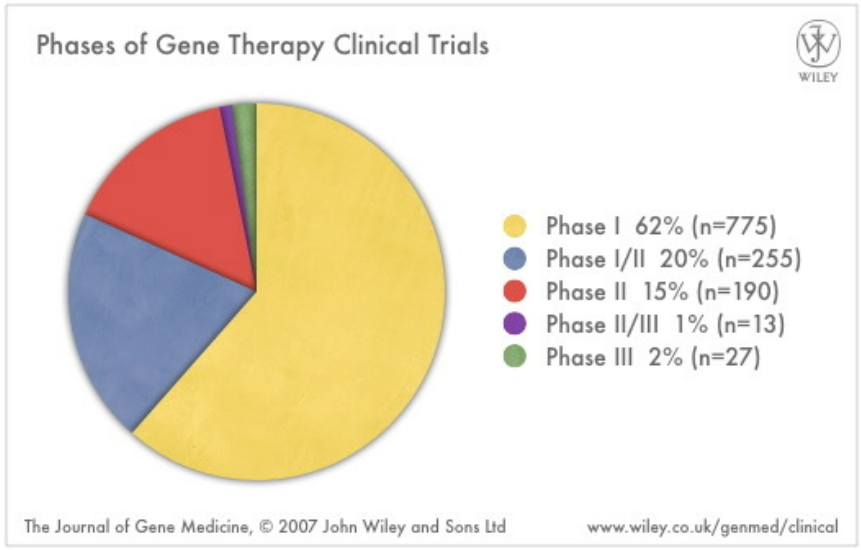
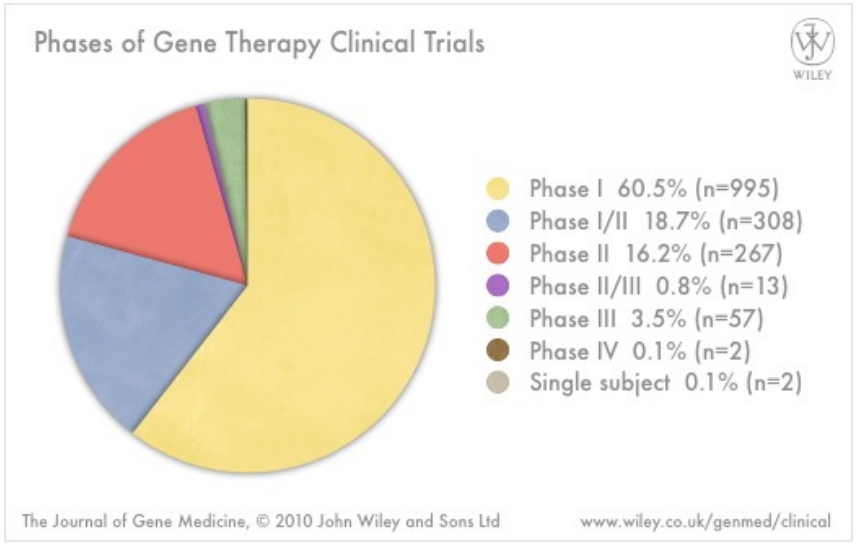
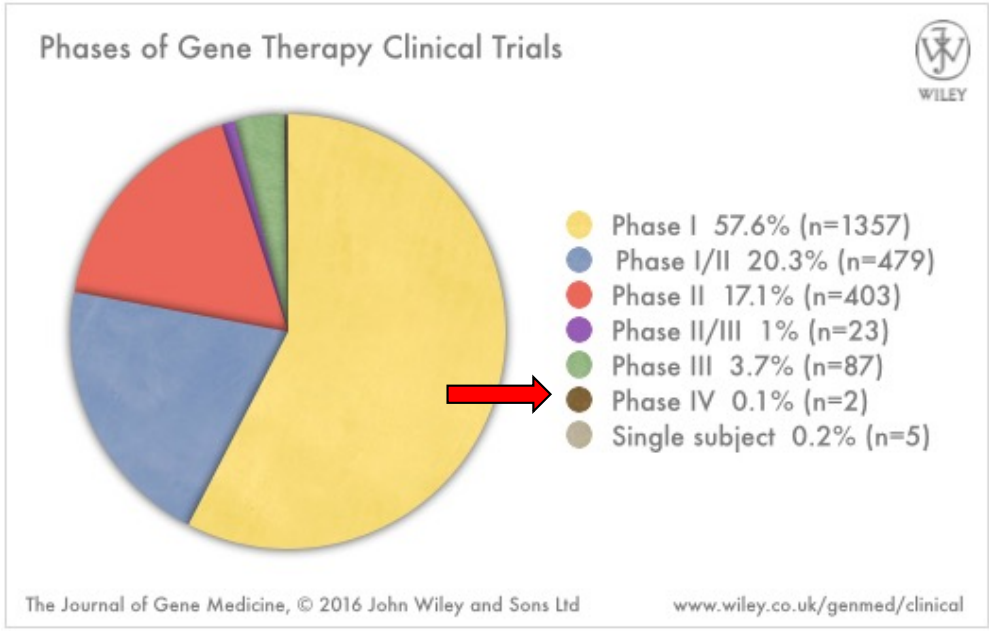


Country	Gene Therapy Clinical Trials	
	Number	%
Italy	**25**	**1.1**
France	**52**	**2.2**

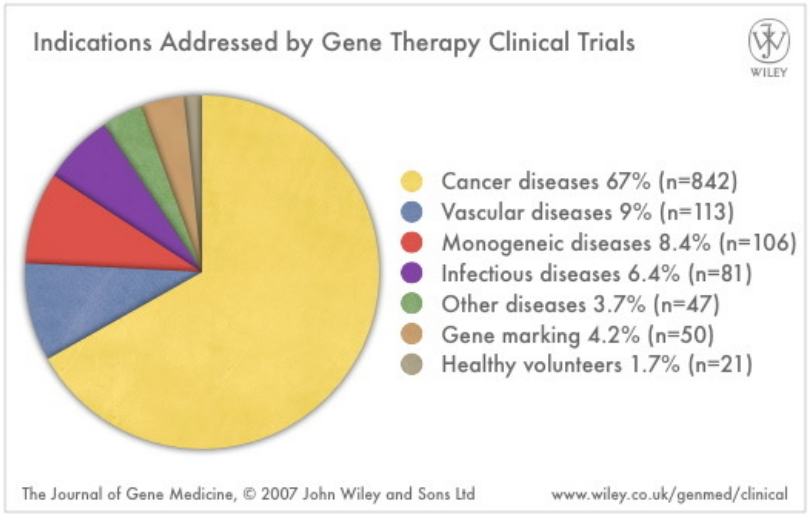
Gene therapy trial phases

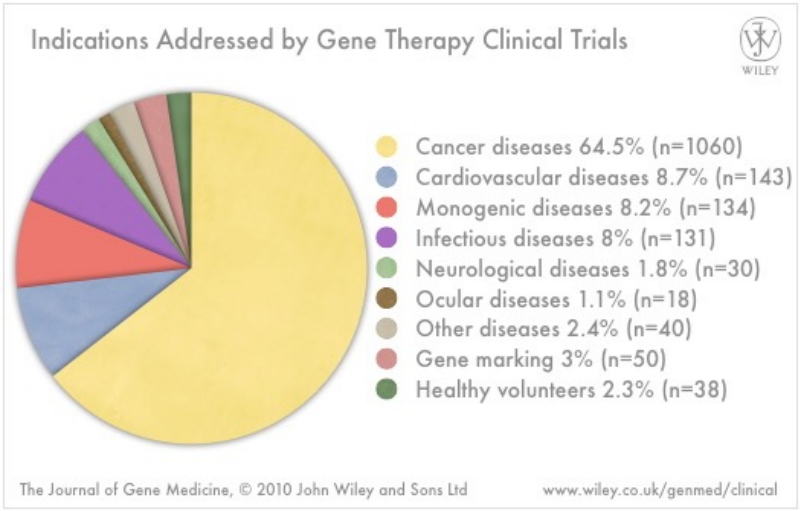


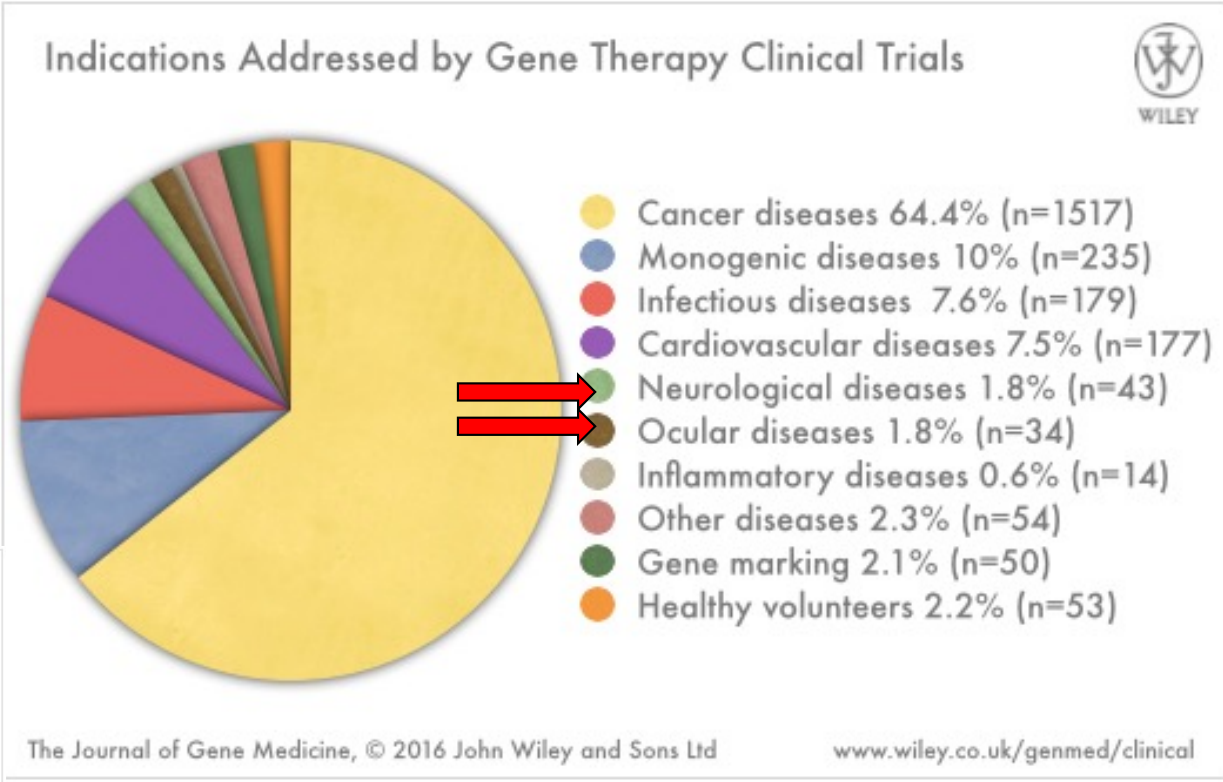




Which diseases with gene therapy



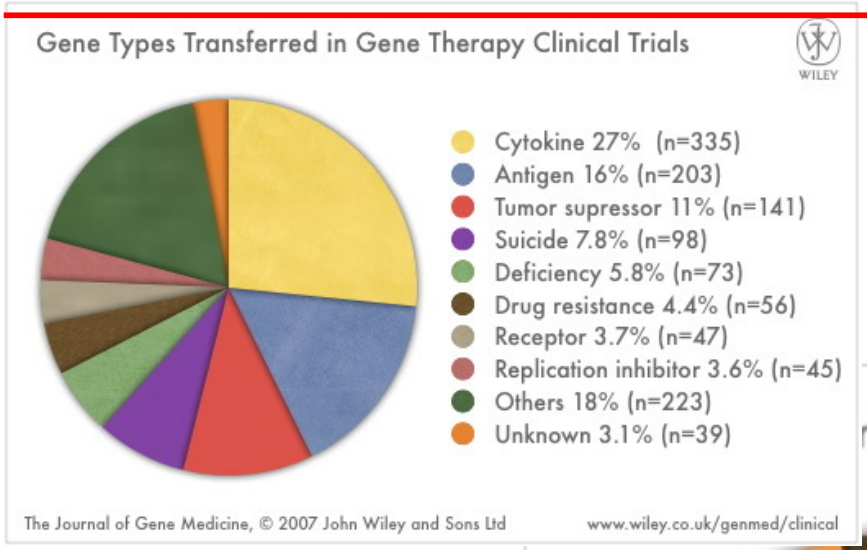


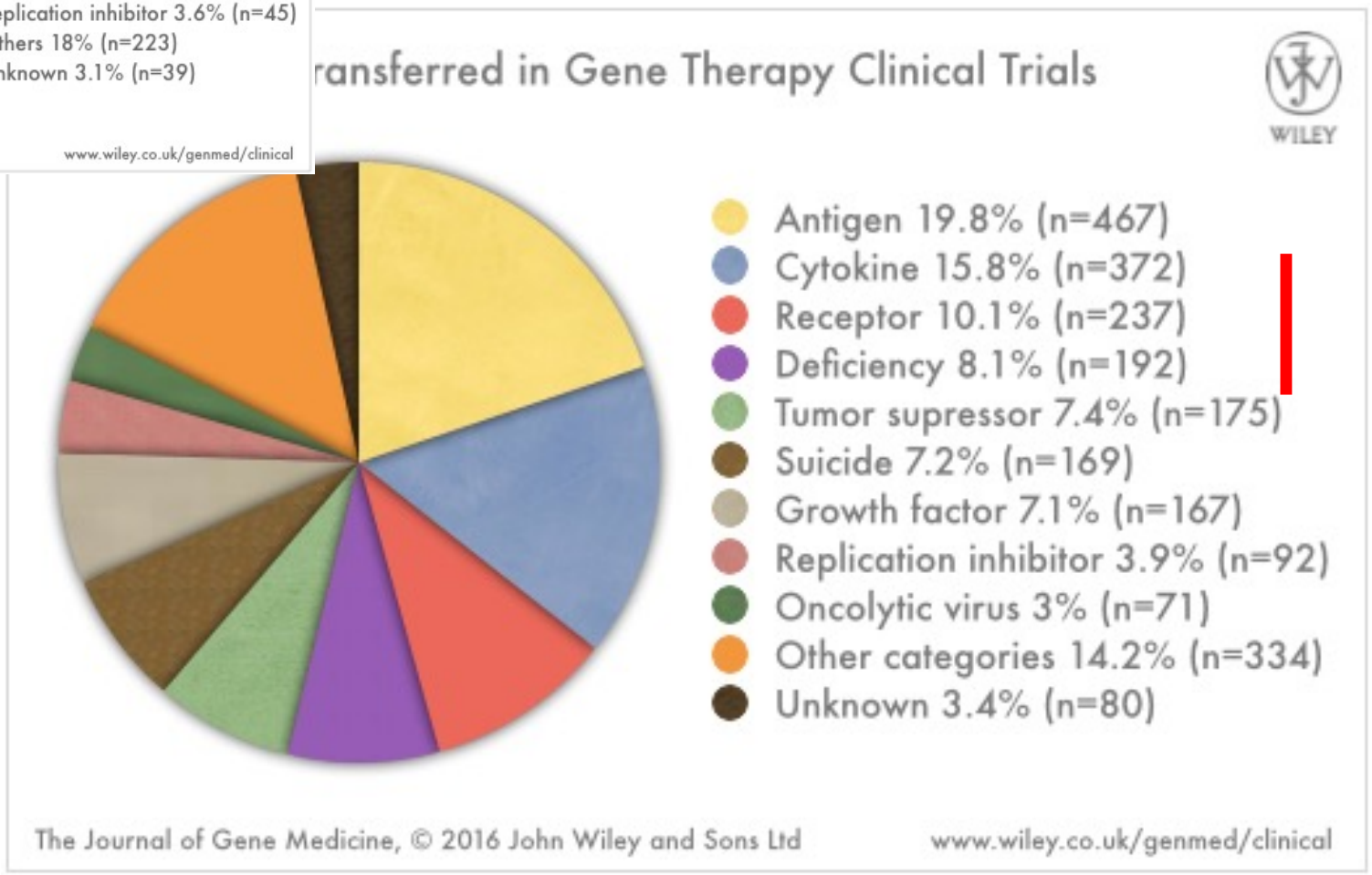


Why such diseases

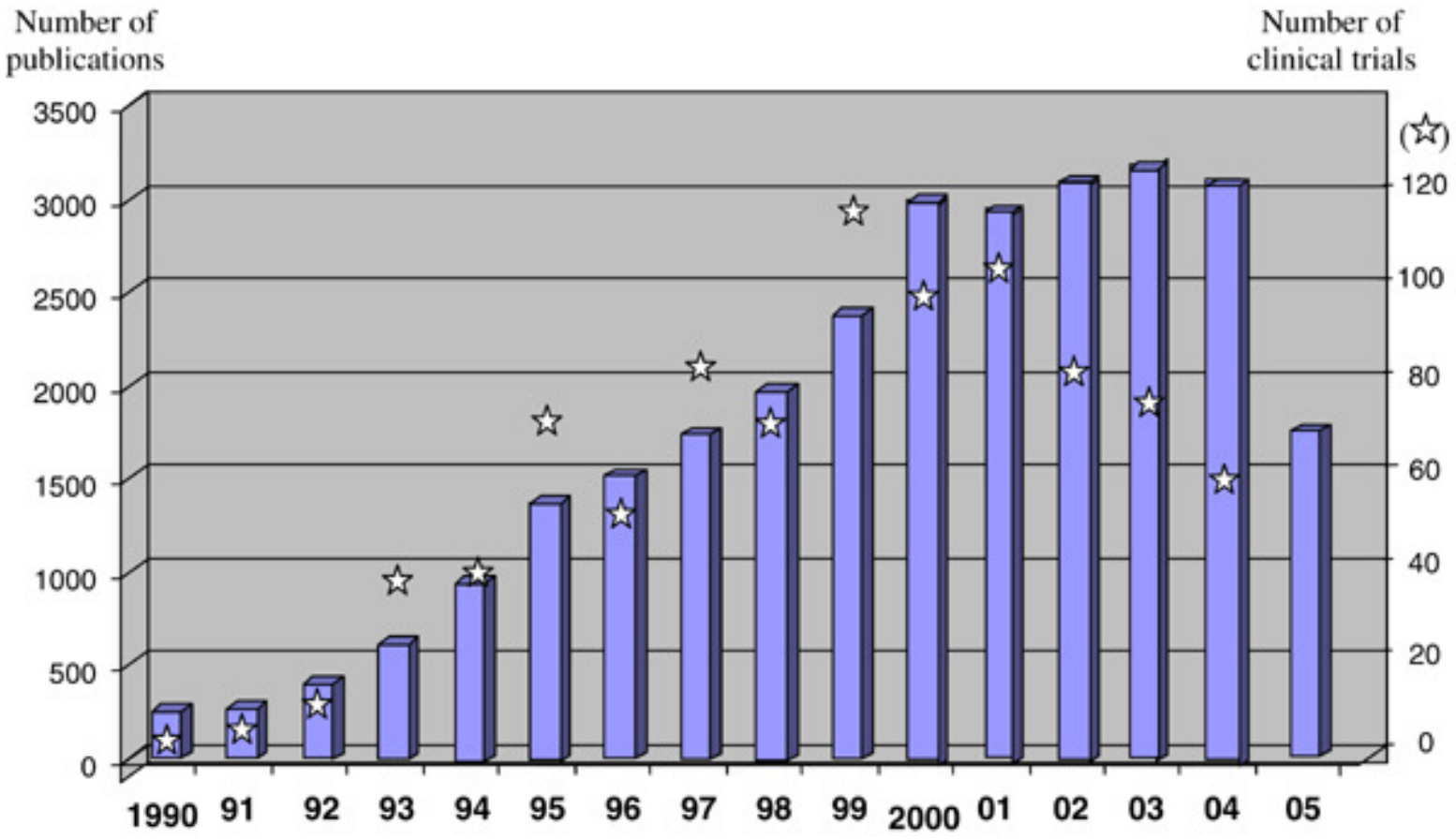
- Killing diseases(:::)
- Known gene
- Accessibility of the hit tissue
- Gene expression not crucial
- Clinically reversible state

Which genes in gene therapy



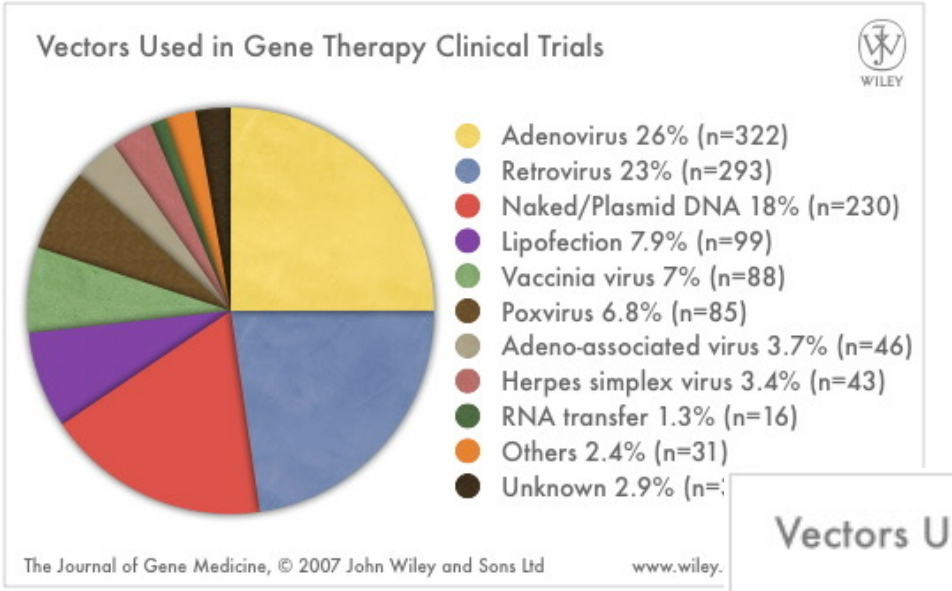


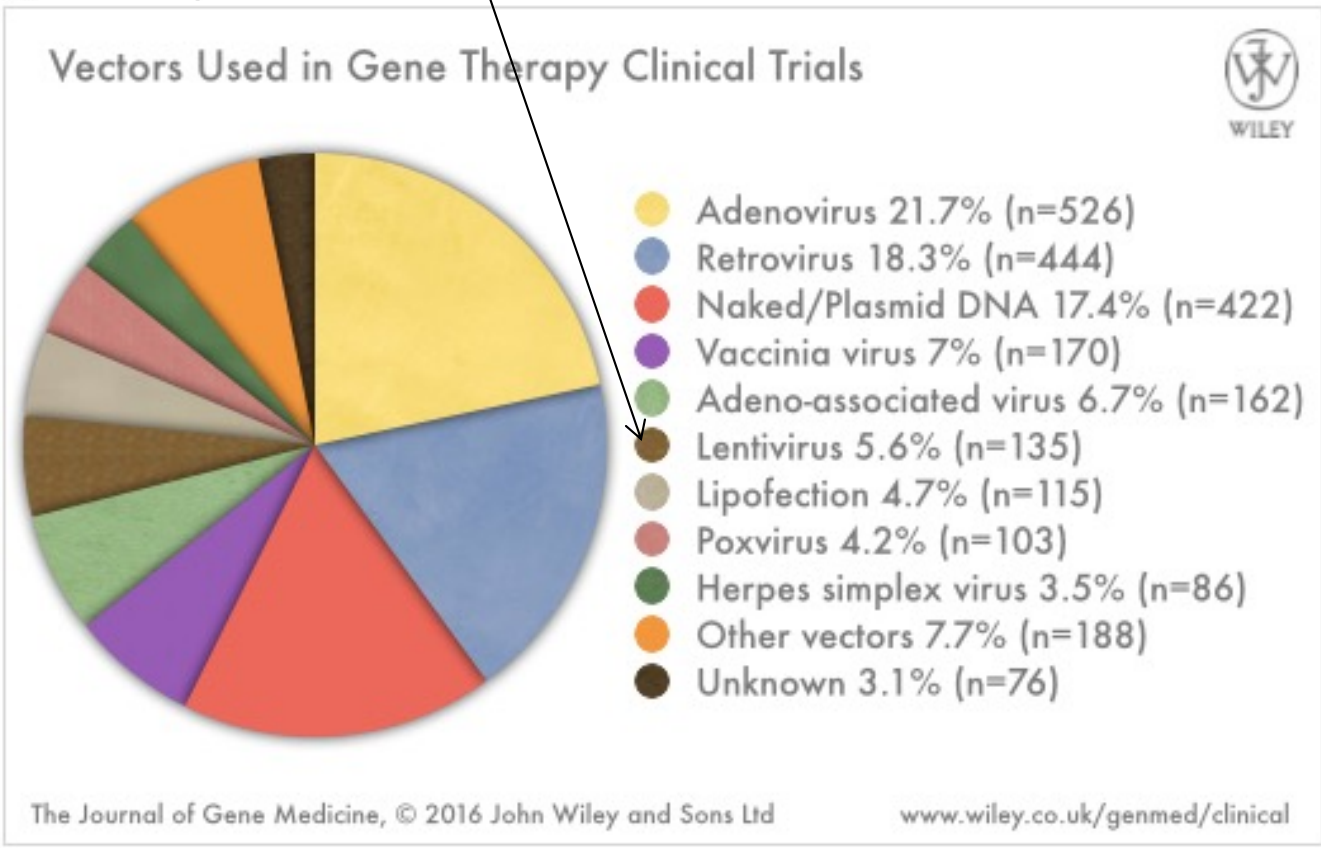
Publications vs clinical trials in gene therapy



Year	Nb of papers	Nb of clin. trials
1990	247	3
91	258	8
92	402	14
93	607	37
94	941	37
95	1354	67
96	1480	51
97	1712	82
98	1945	66
99	2333	117
2000	2947	96
01	2897	103
02	3064	80
03	3102	76
04	3021	58
05	1737	n.a.
TOTAL	28047	895

Which vectors for the genes





Trials in Italy (registered 2013)

Trial ID	Title	disease/transgene	phase	virus/host cell	lab	closed
IT-0001	Treatment of Patients with Severe Combined Immunodeficiency Due to Adenosine Deaminase (ADA) Deficiency by Autologous Transplantation of Genetically Modified T Cells	ADA/ADA	I/II	retro PBL	bordignon milan	1995
IT-0002	Gene Transfer into Peripheral Blood Lymphocytes for In Vivo Immunomodulation of Donor Anti-Tumor Immunity in Patients Affected by Recurrent Disease After Allogeneic BMT	TK/graft versus host disease	I/II	retro PBL	bordignon milan	1995
IT-0003	Gene Transfer into Peripheral Blood Lymphocytes for In Vitro Immunosection and In Vivo Immunomodulation of Donor Anti-Tumor Immunity in Patients Affected by EBV-induced LPD Following Allogeneic BMT	TK/graft versus host disease	I/II	retro PBL	bordignon milan	1995
IT-0004	Active Immunization of Metastatic Melanoma Patients with Interleukin-4 Transfected, Allogeneic Melanoma Cells. A Phase I?II Study	IL4/melanoma	I/II	retro	cascinelli milan	1995
IT-0005	Gene Therapy for metastatic melanoma	IL2/melanoma	I/II	retro/tumor cell	cascinelli milan	open
IT-0006	Gene Therapy in Patients with Lymphoma and Leukemia	?/leukemia, limphoma	I	naked DNA/muscle cell	fazio rome	open
IT-0007	Active Immunization of Metastatic Melanoma Patients with Interleukin- 4 Transduced, Allogeneic Melanoma Cells. A Phase I? II Study	IL4/melanoma	I/II	retro/tumor cell	parminani milan	1997
IT-0008	Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloblative conditionining	ADA/ADA	I		aiuti milan	open
IT-0009	Gene therapy in patients with melanoma	IL4/melanoma	I		maio aviano	open
IT-0010	Active immunization of metastatic melanoma patients with IL-2 or IL-4 gene transfected, allogeneic melanoma cells	IL2/melanoma	I		belli milan	1997
IT-0011	A phase I-II study of active vaccination with autologous T-lymphocytes transduced with HSV-TK and MAGE-A3 in patients with metastatic melanoma and expression of MAGE-A3	TK/melanoma	I/II	retro/autologous	parmiani milan	open
IT-0012	A Phase I Study to Evaluate the Safety/Tolerability and Immunogenicity of V-930 in Patients with Cancers Expressing HER-2 and/or CEA	HER CEA/Colrectal cancer, lung cancer	I/II	naked DNA/tumor cell	parmiani milan	open
IT-0013	Pilot study of transfer of the FHIT gene into bronchial non-small cell lung cancers	Non-small cell lung cancer	I	Ad/ FHIT	parmiani milan	2002
IT-0014	A phase I/II study of active vaccination with autologous T-lymphocytes transduced with HSV-TK and MAGE-A3 in patients with metastatic melanoma and expression of MAGE-A3	TK/melanoma	I/II	retro/autologous	russo milan	open
IT-0015	Study of the safety and efficacy of hematopoietic stem cells transduced with RevM10polAS (RevM10polAS HSCIP) as therapy for HIV-1 infected persons	HIV-1 RevM10 HIV-1 polAS/HIV	I/II	retro/autologous	lazzarin milan	2003
IT-0016	ADA Gene Transfer Into Hematopoietic Stem/Progenitor Cells for the Treatment of ADA-SCID	ADA/ADA	I/II	retro/CD34	roncarolo milan	open
IT-0018	phase III study: infusion of donor lymphocytes transduced with the suicide gene gene HSV-TK after transplantation of allogenic T-depleted stem cells from a haploidentical donor in patients with haematological malignancies	TK/Leukemia	III	HSV		open
IT-0019	Phase I/II study of hematopoietic stem cell gene therapy with Lentiviral Vectors for the treatment of Metachromatic Leukodystrophy	Arysulfate A/Metachromatic Leukodystrophy	I/II	lenti/-	biffi milan	open
IT-0020	Phase I/II study of hematopoietic stem cell gene therapy with Lentiviral Vectors for the treatment of Wiskott Aldrich Syndrome	/WAS gene	I/II		aiuti milan	open
IT-0021	TK008 Randomized Phase III Trial of Haploidentical HCT With or Without an Add Back Strategy of HSV-Tk Donor Lymphocytes in Patients With High Risk Acute Leukemia	leukemia/tyrosinase	III	HSV	ciceri milan	open
IT-0022	Phase Ib Study to Assess the Safety and Immunogenicity of a Novel HCV Vaccine, Based on the Sequential Injection of Ad6NSmut and MVA-NSmut, Given in Combination With PEG-Interferon Alfa Plus Ribavirin for Re-treatment of Chronic Hepatitis C	HCV/Nsmut	I	Ad-ankara vaccine	brunetto pisa	open

DNA as a drug, ideally...pros

- long term
- treatment of the cause
- specificity
- no side effects

Potential risks of gene therapy

- Insertional mutagenesis leading to cancer
- Recombination of disabled vector resulting in environmental pollution by infectious recombinant virus
- Toxic shock caused by viraemia
- Transfer of non-viral exogenous material
- Contamination with other deleterious viruses or organisms
- Physiological effects of over-expression
- Germ-line transduction?