

Supplementary Table 1. Genetic characteristics of the population at diagnosis.

CHD7= Chromodomain Helicase Dna-binding protein 7; *del* = deletion; *FEZF1* = Family Zinc Finger 1; *FGFR1* = Fibroblast Growth Factor Receptor 1; *GLI2* = Glioma-associated family zinc finger 2; *GNRH_R* = Gonadotropin Releasing Hormone Receptor; *ANOS1* = Kallmann syndrome 1; *SOX2* = Sex determining region Y box 2.

	Pump n = 18 (51.4%)	Injection n = 17 (48.6%)	<i>p</i>
Gene			0.951
None	8 (44%)	10 (59%)	
<i>ANOS1</i>	4 (22%)	1 (6%)	
<i>FGFR1</i>	2 (11%)	0 (0%)	
<i>CHD7</i>	2 (11%)	2 (12%)	
<i>GLI2</i>	1 (6%)	1 (6%)	
<i>SOX2</i>	1 (6%)	0 (0%)	
del 6q24	0 (0%)	1 (6%)	
<i>FEZF1</i>	0 (0%)	1 (6%)	
<i>GNRH_R</i>	0 (0%)	1 (6%)	

Supplementary Table 2. Linear hierarchical model (model №2) representing the increase in penile length values after treatment, featuring the results of univariate and multivariate analyses.

The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (18.815) would correspond to the mean value of penile length in the “Injection” group, without any previous testosterone treatment, at “age zero” and time zero. The increase over time was significantly lower in the “Pump” group ($p = 0.002$). Abbreviation : SD = Standard Deviation; IHH = Isolated Hypogonadotropic Hypogonadism; MRI = Magnetic Resonance Imaging; BOBA = Bilateral Olfactory Bulb Agenesis; EPP = Ectopic Posterior Pituitary gland; UOBA = Unilateral Olfactory Bulb Agenesis; *CHD7*= Chromodomain Helicase Dna-binding protein 7; *del* = deletion; *FEZF1* = Family Zinc Finger 1; *FGFR1* =

Fibroblast Growth Factor Receptor 1; *GLI2* = *Glioma-associated family zinc finger 2*; *GNRH_R* = *Gonadotropin Releasing Hormone Receptor*; *ANOS1* = *Kallmann syndrome 1*; *SOX2* = *Sex determining region Y box 2*; LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone.

		Univariate			Multivariate		
		Estimate	SD	p-value	Estimate	SD	p-value
					18.8	1.8	
Pump		2.965	2.278	0.202	1.22	2.14	0.571
Pump * Time					-0.06	0.02	0.002
Time		0.115	0.007	< 0.001	0.16	0.02	< 0.001
IHH		1.018	2.298	0.661			
Age		0.476	0.092	< 0.001	0.23	0.08	0.005
MRI							
	BOBA	-0.749	4.011	0.853			
	EPP	0.977	3.450	0.779			
	UOBA	-2.278	5.091	0.658			
	Other	-3.800	5.497	0.496			
Cause							
	CHD7	-1.507	3.888	0.701			
	del 6q24	-9.151	8.116	0.270			
	FEZF1	-5.651	7.282	0.445			
	FGFR1	-2.651	4.519	0.563			
	GLI2	-0.740	5.039	0.884			
	GNRH_R	-3.651	8.116	0.657			
	ANOS1	-2.533	3.305	0.450			
	SOX2	-3.651	6.339	0.570			
Time hCG/EE		0.013	0.023	0.585			
Time GonadF		0.033	0.022	0.145			

Testosterone before treatment	11.669	3.400	0.002	8.8	3,3	0,013
LH	13.125	8.370	0.127			
LH peak	1.764	1.222	0.177			
FSH peak	0.280	0.062	< 0.001			

Supplementary Table 3. Linear hierarchical model (model №3) representing the increase in penile width values after treatment, featuring the results of univariate and multivariate analyses.

The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (8.544) would correspond to the mean value of penile width in the “Injection” group, without any previous testosterone treatment, at “age zero” and time zero. The increase was not significantly different between both groups ($p = 0.169$). See legends of Supp. Table 2 for abbreviations.

	Univariate			Multivariate		
	Estimate	SD	p-value	Estimate	SD	p-value
				8.5	1	
Pump	0.870	0.976	0.379	0.2	1.2	0.844
Pump * Time				-0.02	0.01	0.169
Time	0.032	0.005	< 0.001	0.05	0.01	< 0.001
IHH	1.394	0.955	0.154			
Age	0.091	0.043	0.037	0.001	0.04	0.982
MRI						
	BOBA	-1.223	1.913	0.529		
	EPP	-2.210	1.750	0.219		
	UOBA	-3.522	2.295	0.138		
	Other	-3.533	4.142	0.402		
Cause						

	CHD7	-1.241	1.530	0.425			
	del 6q24	-1.956	3.802	0.611			
	FEZF1	3.044	3.802	0.431			
	FGFR1	0.940	1.693	0.584			
	GLI2	-3.488	1.94	0.086			
	GNRH_R	1.044	2.978	0.729			
	ANOS1	-0.835	1.258	0.513			
	SOX2						
	Time hCG/EE	0.003	0.010	0.745			
	Time GonadF	0.004	0.009	0.632			
	Testosterone before treatment	3.758	1.312	0.007	3.8	1.5	0,014
	LH	5.290	8.838	0.183			
	LH peak	-0.126	0.555	0.827			
	FSH peak	0.121	0.317	0.716			

Supplementary Table 4. Linear hierarchical model (model №5) representing the increase in testis length values after treatment, featuring the results of univariate and multivariate analyses.

The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (9.604) would correspond to the mean value of testis length in the “Injection” group, with no causes founded, at “age zero” and time zero. The increase was not significantly different between both groups ($p = 0.601$). See legends of Supp. Table 2 for abbreviations.

	Univariate			Multivariate		
	Estimate	SD	p-value	Estimate	SD	p-value
				9.6	1.8	
Pump	3.463	1.256	0.011	0.1	1.7	0.942

Pump * Time				0.01	0.02	0.601	
Time		0.053	0.005	< 0.001	0.04	0.02	0.063
IHH		-1.459	1.331	0.283			
Age		0.210	0.065	0.002	0.17	0.07	0.017
MRI							
	BOBA	5.112	2.758	0.079			
	EPP	4.096	2.325	0.094			
	UOBA	3.895	2.955	0.203			
	Other	-2.042	3.635	0.581			
Cause							
	CHD7	0.671	2.780	0.812	-5	2.3	0.044
	del 6q24	-7.329	3.675	0.061	-3.7	3.2	0.259
	FEZF1	-4.329	2.780	0.137	-3.8	2.6	0.165
	FGFR1	2.171	1.898	0.268	1.2	1.6	0.471
	GLI2	5.363	1.849	0.009	4	1.6	0.021
	GNRH_R	-4.329	3.675	0.254	-0.06	2.9	0.982
	ANOS1	0.093	1.188	0.938	0.6	1	0.575
	SOX2	-4.329	3.675	0.254	-0.9	2.9	0.741
Time hCG/EE		0.040	0.012	0.002	0.06	0.03	0.068
Time GonadF		0.038	0.012	0.004	-0.06	0.03	0.077
Testosterone before treatment		2.743	2.657	0.312			
LH		10.139	7.796	0.211			
LH peak		-1.027	0.610	0.143			
FSH peak		-0.380	0.137	0.032			

Supplementary Table 5. Linear hierarchical model (model №6) representing the increase in testis width values after treatment, featuring the results of univariate and multivariate analyses.

The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (7.045) would correspond to the mean value of testis width in the “Injection” group, without any previous testosterone treatment, at “age zero” and time zero. The increase was not significantly different between both groups ($p = 0.677$). See legends of Supp. Table 2 for abbreviations.

		Univariate			Multivariate		
		Estimate	SD	p-value	Estimate	SD	p-value
					7.04	0.6	
Pump		0.870	0.976	0.379	0.7	0.7	0.337
					-0.005	0.01	0.677
Time		0.032	0.004	< 0.001	0.02	0.01	0.055
IHH		1.394	0.955	0.154			
Age		0.091	0.043	0.037	0.05	0.03	0.071
MRI							
	BOBA	-1.223	1.913	0.529			
	EPP	-2.210	1.750	0.219			
	UOBA	-3.522	2.295	0.138			
	Other	-3.533	4.142	0.402			
Cause							
	CHD7	-1.241	1.530	0.425			
	del 6q24	-1.956	3.802	0.611			
	FEZF1	3.044	3.802	0.431			
	FGFR1	0.940	1.693	0.584			
	GLI2	-3.488	1.949	0.086			
	GNRH_R	1.044	2.978	0.729			
	ANOS1	-0.835	1.258	0.513			
	SOX2						
Time hCG/EE		0.003	0.010	0.745			
Time GonadF		0.004	0.009	0.632			

Testosterone before treatment	3.758	1.312	0.007	1.1	1.2	0,383
LH	5.290	3.838	0.183			
LH peak	-0.126	0.555	0.827			
FSH peak	0.121	0.317	0.716			

Supplementary Table 6. Linear hierarchical model (model №7) representing the increase in testis volume values after treatment, featuring the results of univariate and multivariate analyses. The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (0.034) would correspond to the mean value of testis volume in the “Pump” group, with no causes founded, at “age zero” and time zero. There was not enough data in the “Injection” group to compare it to the “Pump” group. The increase over time in testis volume in the “Pump” group was significantly different to zero ($p < 0.001$). See legends of Supp. Table 2 for abbreviations.

	Univariate			Multivariate		
	Estimate	SD	p-value	Estimate	SD	p-value
				0.03	0.21	
Pump						
Pump * Time						
Time	0.005	0.001	< 0.001	0.005	0.001	< 0.001
IHH	-0.061	0.157	0.701			
Age	0.013	0.007	0.061	0.01	0.005	0.043
MRI						
BOBA	0.553	0.316	0.099			
EPP	0.404	0.298	0.194			
UOBA	0.627	0.431	0.166			
Other	0.243	0.368	0.519			
Cause						

	CHD7	0.196	0.210	0.363	-0.08	0.15	0.611
	del 6q24						
	FEZF1	-0.396	0.374	0.303	-0.18	0.30	0.549
	FGFR1	0.531	0.169	0.006	0.44	0.11	0.001
	GLI2	1.503	0.374	0.001	1.33	0.27	< 0.001
	GNRH_R						
	ANOS1	0.215	0.162	0.201	0.18	0.11	0.125
	SOX2	0.086	0.203	0.676	-0.03	0.12	0.794
	Time hCG/EE	0.004	0.002	0.014	0.003	0.003	0.252
	Time GonalF	0.004	0.002	0.030	-0.003	0.003	0.231
	Testosterone before treatment	-0.408	0.214	0.069			
	LH	0.142	0.145	0.342			
	LH peak	-0.015	0.023	0.541			
	FSH peak	-0.001	0.006	0.979			

Supplementary Table 7. Linear hierarchical model (model №8) representing the increase in testosterone after treatment, featuring the results of univariate and multivariate analyses. The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (1.242) would correspond to the mean value of testosterone in the “Injection” group at time zero. The increase was significantly lower in the “Pump” group ($p = 0.001$). See legends of Supp. Table 2 for abbreviations.

	Univariate			Multivariate		
	Estimate	SD	p-value	Estimate	SD	p-value
				1.2	0.48	
Pump	-0.722	0.561	0.207	-0.28	0.67	0.685
Pump * Time				-0.03	0.008	0.001
Time	0.012	0.003	< 0.001	0.04	0.007	< 0.001
IHH	-0.483	0.571	0.404			

Age		-0.031	0.021	0.139
MRI				
	BOBA	0.714	0.993	0.478
	EPP	1.411	0.844	0.107
	UOBA	1.575	1.327	0.246
	Other	0.315	1.343	0.816
Cause				
	CHD7	-0.897	0.883	0.319
	del 6q24	-1.125	1.752	0.526
	FEZF1	-1.490	1.673	0.381
	FGFR1	-0.696	1.148	0.549
	GLI2	-0.061	1.288	0.962
	GNRH_R	0.145	1.876	0.939
	ANOS1	0.789	0.803	0.335
	SOX2	-1.165	1.578	0.467
Time hCG/EE		-0.006	0.006	0.266
Time GonadF		-0.006	0.005	0.264
Testosterone before treatment		-1.186	0.996	0.242
LH		0.183	0.093	0.059
LH peak		-0.019	0.015	0.233
FSH peak		-0.004	0.005	0.423

Supplementary Table 8. Linear hierarchical model (model №9) representing the increase in AMH after treatment, featuring the results of univariate and multivariate analyses. The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (493.981) would correspond to the mean value of AMH in the “Injection” group, with a normal MRI, with a treatment duration of zero, at time zero. The increase was not significantly different in both groups ($p = 0.546$). See legends of Supp. Table 2 for abbreviations.

		Univariate			Multivariate		
		Estimate	SD	p-value	Estimate	SD	p-value
					494	307	
Pump		498.218	92.920	< 0.001	589	304	0.065
Pump * Time					-0.7	1.1	0.546
Time		3.470	0.386	< 0.001	3.6	1.02	< 0.001
IHH		-41.926	125.358	0.740			
Age		7.028	4.867	0.151			
MRI							
	BOBA	328.382	210.788	0.131	-22	179	0.902
	EPP	435.251	177.526	0.021	137	154	0.380
	UOBA	490.690	285.332	0.097	246	221	0.278
	Other	197.634	285.680	0.495	-88	223	0.695
Cause							
	CHD7	-67.496	198.357	0.736			
	del 6q24	-228.885	371.069	0.543			
	FEZF1	-293.560	364.204	0.427			
	FGFR1	305.873	260.981	0.252			
	GLI2	305.525	274.786	0.276			
	GNRH_R	-126.394	382.238	0.743			
	ANOS1	77.931	177.601	0.664			
	SOX2	34.468	356.196	0.924			
Time hCG/EE		4.241	1.027	< 0.001	-2.2	2.4	0.364
Time GonadF		4.177	0.969	< 0.001	-0.5	2.1	0.811
Testosterone before treatment		-143.770	220.444	0.519			
LH		300.244	285.970	0.302			
LH peak		-5.586	66.067	0.934			
FSH peak		-15.216	19.036	0.443			

Supplementary Table 9. Linear hierarchical model (model №10) representing the increase in Inhibin B after treatment, featuring the results of univariate and multivariate analyses. The reference classes were: “MRI = Normal” and “Cause = None”; the intercept value (116.594) would correspond to the mean value of Inhibin B in the “Injection” group, with a normal MRI, with a treatment duration of zero, at time zero. The increase was not significantly different in both groups ($p = 0.066$). See legends of Supp. Table 2 for abbreviations.

	Univariate			Multivariate		
	Estimate	SD	p-value	Estimate	SD	p-value
				117	150	
Pump	172.243	49.106	0.001	133	148	0.379
Pump * Time				-1.2	0.6	0.066
Time	1.968	0.180	< 0.001	2.8	0.6	< 0.001
IHH	22.960	56.842	0.689			
Age	3.575	2.270	0.117			
MRI						
BOBA	171.673	92.063	0.097	77	88	0.391
EPP	190.433	78.063	0.022	107	76	0.171
UOBA	182.259	121.858	0.147	115	107	0.294
Other	118.277	123.724	0.348	47	109	0.669
Cause						
CHD7	-1.820	91.506	0.984			
del 6q24						
FEZF1	-174.403	163.198	0.295			
FGFR1	16.796	115.340	0.885			
GLI2	65.946	131.444	0.620			
GNRH_R	-161.203	184.949	0.391			
ANOS1	29.260	79.520	0.716			

	SOX2	-80.918	158.718	0.614			
Time hCG/EE		1.452	0.527	0.010	-1.4	1.2	0.250
Time GonalF		1.633	0.473	0.002	0.5	1.02	0.603
Testosterone before treatment		-49.013	98.559	0.622			
LH		186.613	65.279	0.008			
LH peak		-7.741	13.078	0.568			
FSH peak		-2.700	3.889	0.505			