How to become a genomics GENie:

Presenting GenQA's online education platform that offers training and ongoing competency assessment

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Introduction

The increase in genomic testing is generating a vast amount of genomic data which needs to be analysed and interpreted so relevant clinical findings are reported.

To be able to deliver this, there is an increasing need for individuals to demonstrate their competency to **perform data analysis and report genomic test results.** As variant classification guidance is evolving and variant nomenclature frequently being updated, it is becoming more challenging to keep abreast of changes and evidence up to date knowledge.

To support the genomics workforce, GenQA introduced **the Genomics Individual Education platform, GENie,** which builds on GenQA's extensive expertise in providing individual competency assessment already used by **50,000 participants.**

The participation and outcomes of the modules to support the **accurate classification** of single nucleotide variants (SNVs) and copy number variants (CNVs), and the **standardised use of HGVS nomenclature and ISCN** are presented.

Methods

- The online GENie platform provides independent assessment of competency for a range of tasks performed by the genomic workforce.
- **Nomenclature:** There are two modules supporting the accurate use of standardised nomenclature; Human Genome Variation Society (HGVS)[1] and International System for Human Cytogenomic Nomenclature (ISCN)[2].
- **Variants:** Separate modules are provided for SNV and CNV pathogenic classification classified by an expert panel according to ACMG guidelines[3,4].
- Randomised variants are presented to the participants as sequencing traces, ideograms or written description, to either interpret into standardised nomenclature or for classification of pathogenicity (Figure 1).

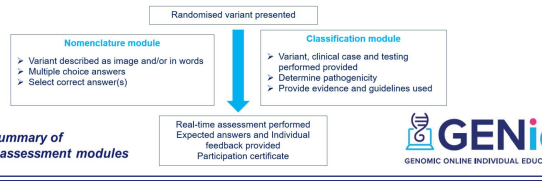


Figure 1 – Summary of competency assessment modules

Variant Classification Results

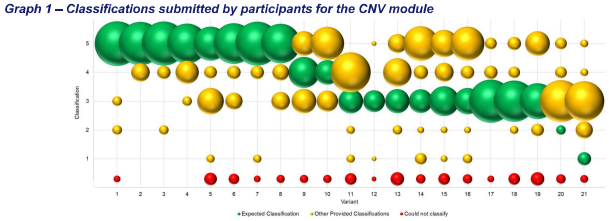
Participation

The SNV module was completed by over 498 participants and 484 completed the CNV module.

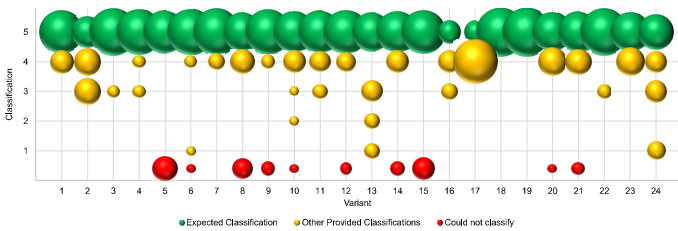
Classification of SNVs and CNVs

The classification submitted by the participants for each of the 21 CNVs with an expected pathogenic classification is represented by bubbles (Graph 1), the size of which corresponds to the percentage of participants who reported the expected classification (green), or incorrect classification (yellow), or could not classify the variant (red). Fifty SNVs were presented to participants and Graph 2 displays the classifications of the 24 Class 5 variants and Graph 3 presents the participants' classification of the Class 1 to 4 variants.

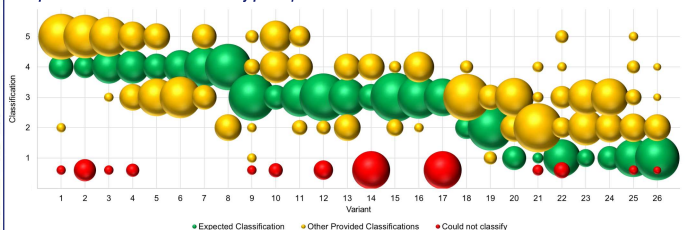
Graph 1 – Classifications submitted by participants for the CNV module



Graph 2 – Classifications submitted by participants for the SNV module – Class 5 variants



Graph 3 – Classifications submitted by participants for the SNV module – Classes 1 to 4 variants



Variability

Participant classifications of the CNVs were variable with the challenging variants of uncertain significance giving the widest range of classifications, particularly variants 11, 14, 15 and 16 (Graph 1). The classification of pathogenic SNVs (Graph 2) was generally standardised with the majority of alternative classifications being likely pathogenic (Class 4).

However, some variants (#10, #13 and #24) were more challenging ranging from benign/likely benign through to pathogenic. This was also observed for the remaining SNVs (Graph 3) where many variants were classified across all five categories.

Table 1 – Variants used in the Variant classification modules

	Graph 2 CNVs	Graph 3 SNVs	Graph 4 SNVs
1	arr[GRCh37] 10p15.3 (100047_468133)x1	*ADGRV1* NM_032119.4:c.176887>G p.(Tyr5896Ter)	*BRCA1* NM_007294.4:c.5478_5479dup p.(Met1827fs)
2	arr[GRCh37] 15q13.2q13.3 (31073668_32444261)x1	*AIRE* NM_000383.4:c.769C>T p.(Arg257Ter)	*APP* NM_000484.4:c.2150T>G p.(Val717Gly)
3	arr[GRCh37] 17q21.31(43710151_44163085)x1	*AIRE* NM_000383.4:c.967_979del p.(Leu323fs)	*CASR* NM_000388.4:c.659G>A p.(Arg220Gln)
4	arr[GRCh37] 21q21.1q22.11(17671957_32118245)x1	*ALPK3* NM_020778.5:c.4688G>A p.(Trp1563Ter)	*DMD* NM_004006.3:Exons 27 to 28 duplication
5	arr[GRCh38] 15q11.2(22693148_23088545)x1 mat	*BRCA1* NM_007294.4:c.3820del p.(Val1274Ter)	*FGFR2* NM_000141.5:c.1070T>C p.(Leu357Ser)
6	arr[GRCh38] 18q22.1q23(65485559_80255845)x1	*CFTR* NM_000492.3:c.1521_1523del p.(Phe508del)	*FLT4* NM_182925.5:c.2674G>C p.(Ala892Pro)
7	arr[GRCh38] Xq11.2(gnh11.22(49455511_52597147)x3	*CFTR* NM_000492.3:c.2490+1G>A	*LARGE1* NM_004737.4:c.1525G>A p.(Glu509Lys)
8	arr[GRCh38] Xq28(154890368_155331063)x2 mat	*CFTR* NM_000492.3:Exons 12-18 deletion	*MEN1* NM_130799.2: c.1663_1664del p.(Ser555Ter)
9	arr[GRCh37] 20q11.21q11.22(29906675_33192526)x3	*CFTR* NM_000492.3:Exons 2-3 deletion	*SRD5A3* NM_024592.5:c.608A>C p.(His203Pro)
10	arr[GRCh38] 1p33q32.3(48110723_54999200)x3	*COL2A1* NM_001844.5:c.1636G>A p.(Gly546Ser)	*RYR2* NM_001035.3:c.7099G>A p.(Gly2337Arg)
11	arr[GRCh37] 1q22(155394494_155708622)x3	*COL5A1* NM_000093.5:c.3762del p.(Gly1255Alafs)	*RAD51D* NM_002878.4:c.96dup p.(Thr32fs)
12	arr[GRCh37] 9q31.1(103872849_104979571)x3	*DOCK6* NM_020812.4: c.5939+2T>C	*ALPK3* NM_020778.5:c.4372A>T p.(Thr1458Ser)
13	arr[GRCh37] Xq27.1q27.3(139490779_144317943)x3	*GALT* NM_000155.4:c.563A>G p.(Gln188Arg)	*APOB* NM_000384.2:c.13480_13482del p.(Gln4494del)
14	arr[GRCh38] 15q11.2(22693148_23088545)x1	*GJB1* NM_000166.6:c.658C>T p.(Arg220Ter)	*ATM* NM_000051.4:c.7515+2C>T
15	arr[GRCh38] 17q12(36792631_37854407)x3 dn	*HRAS* NM_005343.4:c.173C>T p.(Thr58Ile)	*BMPR2* NM_001204.6:c.797G>C p.(Arg266Thr)
16	arr[GRCh38] 1q21.1(145639445_146018623)x1 dn	*LARGE1* NM_004737.4 Exons 4 to 6 deletion	*COL4A5* NM_033380.3:c.2877_2879del p.(Leu960del)
17	arr[GRCh38] 3q22.1q22.2(132296686_135623644)x3 dn	*NF2* NM_000268.4:c.586C>T p.(Arg196Ter)	*PALB* NM_024675.4:c.2734T>G p.(Trp912Gly)
18	arr[GRCh38] 5q22.2(112750708_112780733)x3	*PALB2* NM_024675.4:c.172_175del p.(Gln60Argfs Ter)	*BRCA2* NM_000059.4:c.202A>G p.(Lys68Glu)
19	arr[GRCh38] Xp21.3p21.2(29023875_29283048)x1	*PALB2* NM_024675.4:c.3549C>G p.(Tyr1183Ter)	*BRCA2* NM_000059.4:c.9271G>A p.(Val3091Ile)
20	arr[GRCh38] 6q15q16.1(96063179_93827538)x3 dn	*POLG* NM_002693.2:c.2209G>C p.(Gly737Arg)	*BRCA2* NM_000059.4:c.9501+3A>T
21	arr[GRCh37] 1q44 (247,815,979_246,609,997)x1	*RET* NM_020975.4:c.2551del p.(Leu851Serfs)	*ATM* NM_000051.4:c.2442C>A p.(Asp814Glu)
22	arr[GRCh37] 10p15.3 (100047_468133)x1	*SH3TC2* NM_024577.4:c.2860C>T p.(Arg954Ter)	*BRCA1* NM_007294.4:c.1106_1108del p.(Asp369del)
23		*SH3TC2* NM_024577.4:c.386-2A>C p.(?)	*BRCA1* NM_007294.4:c.661G>T p.(Ala221Ser)
24		*TTR* NM_000371.4:c.424G>A p.(Val142Ile)	*BRCA2* NM_000059.4:c.9501+3A>T
25			*FBN1* NM_000138.4:c.6832C>T p.(Pro2278Ser)
26			*NF1* NM_000267.3:c.846G>A p.(=)

Nomenclature Results

Participation

Globally 822 participants completed the HGVS module and 708 completed the ISCN module.

HGVS nomenclature

The standard of use of HGVS nomenclature[1] was high with 8 of the 10 variants being correctly described by >75% of participants (Graph 4). Table 2 summarises the expected answers and the most common errors submitted.

Variants 5 and 8 had the highest error rate because participants listed the reference sequences in the incorrect order. The NC record (related to the plus strand) should be listed before the NM record (coding strand).

The variants displayed as sequencing traces resulted in incorrect base changes or base numbering.

Other common errors were omission of the reference sequence version number or the inclusion of deleted bases.

Graph 4 – Results of the HGVS Nomenclature module

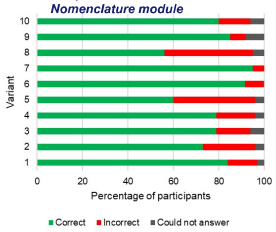


Table 2 – Results of the HGVS Nomenclature module

Variant	Correct Nomenclature	Most frequent error	
1	NM_000527.4:c.1284C>G	NM_000527.4:c.1284**G>C**	Incorrect base change
2	NM_000527.4:c.660_669del	NM_000527.4 c.660_669del**ACCTGGAATA**	Inclusion of deleted bases
3	NM_001114753.1:c.145G>T p.(Val49Phe)	NM_001114753.1:c.145**T>G** p.(Val49Phe)	Incorrect base change
4	NM_000384.3:c.4951G>A p.(Gly1651Arg)	NM_000384.3:c.4951**C>T**	Incorrect base change
5	NC_000009.12(NM_001114753.3):c.360+1G>A	**NM_001114753.3(NC_000009.12)**:c360+1G>A	Incorrect order of reference sequence
6	NM_007294.4:c.5503_5564del	NM_**007294:c.5503_5564del**	No version number for the reference sequence
7	NM_002834.5:c.417G>C	NM_**002834**:c.417G>C	No version number for the reference sequence
8	NC_000019.10(NM_000215.4):c.2350+1G>T NC_000019.9(NM_000215.4):c.2350+1G>T NC_000019.10:g.17834570C>A NC_000019.9:g.17945379C>A	**NM_000215.4(NC_000019.10)**:c.2350+1G>T	Incorrect order of reference sequence
9	NM_001114753.1:c.1134G>A NM_001114753.3:c.1134G>A	NM_001114753.1:c.113**3**G>A	Incorrect number of base
10	NM_004006.2:c.2376G>C(;)3103del	**NM_004006.2:c.[2376G>C];[3103delT>A]**	Incorrect format

ISCN

The correct application of ISCN 2020[2] was most consistent for reporting microarray results, variants 9 & 10, and neoplasia karyotyping, variants 5 & 6 (Graph 5 and Table 3).

Table 3 summarises the expected answers and the most common errors submitted.

Reporting neoplasia FISH results, variants 7 & 8 with only approximately 20% and 40% respectively using correct ISCN.

The most frequent error for many of the variants was inappropriate use of spaces. However, for the constitutional FISH variant 4 the presence of the additional space after the abbreviation 'nuc ish' will be correct according to the most recent release of ISCN (ISCN 2024[5]).

Graph 5 – Results of the ISCN module

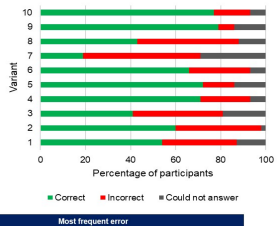


Table 3 – Results of the ISCN Nomenclature module

Variant	Correct Nomenclature	Most frequent error
Constitutional Karyotyping		
1	46,XY,rec(4)dup(4p)inv(4)(p16.1q34.3)dpat	46,XY,**der(4)**dup(4p16.1)del(4)(q34) **der(4)inv**(p16.1q34)pat
2	46,Y,t(X;8)(p22.3;q24.1)	46,**XY**,t(X;8)(p22.3;q24.1)
Constitutional FISH		
3	nuc ish(DXZ1x2,DYZ3x0,D18Z1x2),(RB1,D21S270/D21S1425/D21S341)x2	nuc ish (DXZ1x2,DYZ3x0,DXZ1x2)(**30**),(13q14.2,21q22.13)x2(**30**)
4	nuc ish(DXZ1x2,DYZ3x1,D18Z1x2)[150/200],(RB1x2,D21S270/D21S1425/D21S341x3)	nuc ish (DXZ1x2,DYZ3x1,D18Z1x2)[150/200], (RB1x2,D21S270/D21S1425/D21S341x3)
Neoplasia Karyotyping		
5	48,XX,+8,+22[10]/46,XX[2]	**46,XX[2]/48,XX,+8,+22[10]**
6	46,XY,inv(3)(q21q26)[13]/46,idem,del(7)(q22q376)[4] 46,XY,inv(3)(q21q26)[13]/46,si,del(7)(q272q376)[4]	46,XY,inv(3)(q21q26)[13]/46,**XY**,del(7)(q272q376)[4]
Neoplasia FISH		
7	nuc ish(CDKN2Cx0,CKS1Bx2)[175/200],(FGFR3,IGH)x2[200),(D5S1518E/D5S1976x3,D9S17 83/NR4A3x3,SMAD6x2)[180/200],(5'MYCx3,3'MYCx2)(5'MYC con 3'MYCx1)[190/200], (CCND1,IGH)x2[200],(D13S1477/D13S319/D13525x1,D13S1825x2)[170/200],(IGH,MAF)x2[200],(IGH52,MAFBx1)[190/200],(TP53/EFNB3x1,D17Z1x2)[190/200]	nuc ish(**FGFR3,CCND1,IGH,MAF**)x2[200],(**D5S1518Ex3,D9S1783 x3,RH120302x2**)(180/200),(5'MYCx3,3'MYCx2)(5'MYC con 3'MYCx1)[190/200], (D13S1477x1,D13S1825x2)[170/200],(**IGH52,MAFBx1**)[190/200],(**TP53x1,D17Z1x2**)[180/200]
8	nuc ish(ABL2x2)[100],(PDGFRBx2)(3'PDGFRB sep 5'PDGFRB1)[76/100], (ABL1,BCR)x2[100]	nuc ish(ABL2x2)[100],(PDGFRBx2)(**3'PDGFRB sep 5'PDGFRB1**)[76/100], (ABL1,BCR)x2[100]
Microarrays		
9	arr[GRCh38] 6q21q25.1(113,900,000_149,100,000)x1,(21)x3	arr[GRCh38] (**21**)x3, 6q21q25.1(113,900,000_149,100,000)x1
10	arr[GRCh38] 20q13.13q13.33(51,001,876_64,323,572)x1,22q13.32q13.33 (48,533,211_50,776,368)x3 arr[GRCh36] 20q13.13q13.33(51001876_64323572)x1,22q13.32q13.33 (48533211_50776368)x3	arr[**GRCh38]20q13**.13q13.33(51001876_64323572)x1,22q13.32q13.33(48533211_50776368)x3

Conclusions

As more genomic data is generated then Scientists and Clinicians interpreting the results need to be competent to use **variant classification frameworks** and **standardised nomenclature.** This will be particularly important as the ISCN 2024[5] has recently been published and ACMG are expected to shortly release updated variant classification guidelines.

The uptake in the use of the **GENie platform** proves there is a demand for continued education and the results obtained by participants evidences that there is a variability in the level of competency to accurately determine the pathogenicity of variants and to apply international standardised nomenclature.

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Conflicts of interest: RH is the ISCN Standing Committee Chair.