

## SUPPLEMENTAL MATERIAL

**Supplemental Table 1** – List of Sarcomeric Variants in Patients with HCM and Multiple Pathogenic/Likely Pathogenic Variants. Of the 63 patients, 13 (21%) had HCM-LVSD.

P= Pathogenic, LP= Likely Pathogenic, VUS= Variant of Unknown Significance.

| Patient | HCM-LVSD at anytime | Sarcomeric Variants   |
|---------|---------------------|---|
| 1       | Yes                 | MYBPC3:P p.Glu258Lys(c.772G>A); MYH7:P p.Arg723Cys(c.2167C>T)   |
| 2       | Yes                 | MYBPC3:P p.Glu258Lys(c.772G>A); MYH7:P p.Arg723Cys(c.2167C>T)   |
| 3       | Yes                 | MYBPC3:LP p.Arg502Trp(c.1504C>T); MYBPC3:P c.927-2A>G   |
| 4       | Yes                 | MYBPC3:LP p.Gly531Arg(c.1591G>C); TNNT2:LP p.Phe110Leu(c.330T>G)  |
| 5       | Yes                 | MYBPC3:LP p.Pro371Arg(c.1112C>G); MYBPC3:P p.Lys1065Glufs*12(c.3192dup); MYH7:P p.Arg869His(c.2606G>A)                                      |
| 6       | Yes                 | MYBPC3:P p.Glu258Lys(c.772G>A); MYH7:P p.Arg869His(c.2606G>A);<br>TNNI3:P p.Ala86Glyfs*23(c.257_258del)                                     |
| 7       | Yes                 | MYBPC3:LP p.Pro371Arg(c.1112C>G); MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 8       | Yes                 | MYH7:P p.Gly768Arg(c.2302G>A); TNNT2:P p.Arg285Cys(c.853C>T)  |
| 9       | Yes                 | MYBPC3:LP p.Pro371Arg(c.1112C>G); MYBPC3:VUS p.Arg970Trp(c.2908C>T); MYBPC3:P p.Lys1065Glufs*12(c.3192dup)                                  |
| 10      | Yes                 | MYBPC3:LP p.Pro371Arg(c.1112C>G); MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 11      | Yes                 | MYBPC3:P c.3628-41_3628-17del;TNNI3:LP p.Arg162Trp(c.484C>T);TNNI3:LP p.Arg162Trp(c.484C>T)   |
| 12      | Yes                 | MYBPC3:P p.Tyr797*(c.2391C>A);MYBPC3:P p.Tyr797*(c.2391C>A);PLN:VUS c.2T>C  |
| 13      | Yes                 | DSP:VUS c.3956C>G;MYBPC3:PAT p.Tyr797*(c.2391C>A);MYBPC3:P p.Tyr797*(c.2391C>A);PLN:VUS c.2T>C;TTN:VUS c.67330C>T;TTN:VUS c.89714G>A        |
| 14      | No                  | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)  |
| 15      | No                  | ACTN2:VUS p.Arg572Trp(c.1714C>T);MYBPC3:P p.Arg502Gln(c.1505G>A);MYBPC3:P c.3190+1G>A;TNNT2:P p.Lys210del(c.629_631del)                     |
| 16      | No                  | LAMA4:p.Ala276Asp(c.827_828delinsAC);LAMA4:P p.Ala276Asp(c.827_828delinsAC);<br>TNNT2:PAT p.Trp287*(c.860G>A);TNNT2:PAT p.Trp287*(c.860G>A) |
| 17      | No                  | MYBPC3:P p.Trp818*(c.2524:G>A);MYL3:P p.Arg154His(c.461:G>A)  |
| 18      | No                  | MYBPC3:P p.Pro955Argfs*95(c.2864_2865del);MYH7:P p.Gly1057Asp(c.3170G>A)  |
| 19      | No                  | MYH7:P p.Ala797Thr(c.2389G>A);MYH7:LP p.Arg807His(c.2420G>A)  |
| 20      | No                  | MYH7:LP p.Glu894Gly(c.2681A>G);MYH7:P p.Glu924Lys(c.2770G>A)  |
| 21      | No                  | MYBPC3:P p.Gln1233*(c.3697C>T);MYBPC3:P p.Gln1233*(c.3697C>T)   |

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| 22 | No | MYBPC3:P c.2308+1G>A;MYH7:P p.Val606Met(c.1816G>A)                       |
| 23 | No | MYBPC3:P p.Pro955Argfs*95(c.2864del);MYBPC3:P c.927-9G>A                 |
| 24 | No | MYH7:P c.3100-2A>C;MYH7:LP p.Arg1712Gln(c.5135G>A)                       |
| 25 | No | MYBPC3:P p.Glu334*(c.1000G>T);MYL2:P p.Glu22Lys(c.64G>A)                 |
| 26 | No | MYBPC3:P p.Glu258Lys(c.772G>A);MYH7:P p.Arg694Cys(c.2080C>T)             |
| 27 | No | MYBPC3:P c.772G>C;MYH7:LP p.Lys865Arg(c.2594A>G)                         |
| 28 | No | MYBPC3:P p.Ala392Leufs*14(c.1174del); MYBPC3:LP p.Arg597Trp(c.1789C>T)   |
| 29 | No | MYBPC3:P p.Glu542Gln(c.1624G>C);TNNT2:LP p.Lys66Gln(c.196A>C)            |
| 30 | No | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 31 | No | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 32 | No | MYH7:P p.Thr177Ile(c.530C>T);MYH7:LP p.Ile303Met(c.909C>G)               |
| 33 | No | MYBPC3:P p.Ala392Leufs*14(c.1174del);MYL3:LP p.Gly146Trpfs*7(c.435dup)   |
| 34 | No | MYBPC3:P p.Glu258Lys(c.772G>A);TNNT3:P p.Ala86Glyfs*23(c.257_258del)     |
| 35 | No | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 36 | No | MYBPC3:P p.Ala392Leufs*14(c.1174del);MYBPC3:LP p.Arg597Trp(c.1789C>T)    |
| 37 | No | MYBPC3:P p.Glu258Lys(c.772G>A);MYH7:LP p.Lys865Arg(c.2594A>G)            |
| 38 | No | MYH7:LP p.Met690Thr(c.2069T>C);MYH7:LP p.Asp1869Gly(c.5606A>G)           |
| 39 | No | MYH7:P p.Arg869His(c.2606G>A);TNNT2:P p.Arg286Cys(c.856C>T)              |
| 40 | No | MYBPC3:P c.506-2A>C;MYH7:P p.Arg723Cys(c.2167C>T)                        |
| 41 | No | MYBPC3:P c.506-2A>C;MYH7:P p.Arg723Cys(c.2167C>T)                        |
| 42 | No | MYH7:P p.Gly768Arg(c.2302G>A);TNNT2:P p.Arg285Cys(c.853C>T)              |
| 43 | No | MYBPC3:P p.Glu258Lys(c.772G>A);TNNT2:P p.Arg285Cys(c.853C>T)             |
| 44 | No | MYBPC3:P p.Glu258Lys(c.772G>A);MYH7:P p.Arg869His(c.2606G>A)             |
| 45 | No | MYBPC3:P p.Glu258Lys(c.772G>A);TNNT2:P p.Arg285Cys(c.853C>T)             |
| 46 | No | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 47 | No | MYBPC3:LP p.Pro371Arg(c.1112C>G);MYBPC3:P p.Lys1065Glufs*12(c.3192dup)   |
| 48 | No | MYBPC3:P p.Ala392Leufs*14(c.1174del);MYBPC3:LP p.Arg597Trp(c.1789C>T)    |
| 49 | No | MYBPC3:P p.Glu258Lys(c.772G>A);TNNT2:P p.Arg285Cys(c.853C>T)             |
| 50 | No | MYH7:P p.Ala797Thr(c.2389G>A);MYH7:P p.Gly853fs(c.2558del)               |
| 51 | No | MYBPC3:P p.Pro955Argfs*95(c.2864_2865del); TNNT3:P p.Ala157Val(c.470C>T) |
| 52 | No | MYBPC3:LP p.Arg502Trp(c.1504C>T); MYBPC3:P c.927-9G>A                    |
| 53 | No | MYH7:P p.Ala226Val(c.677C>T);MYH7:P p.Ala226Val(c.677C>T)                |

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| 54 | No | MYH7:LP p.His581Arg(c.1742A>G); MYH7:P p.Gly584Ser(c.1750G>A)   |
| 55 | No | MYH7:LP p.His581Arg(c.1742A>G); MYH7:P p.Gly584Ser(c.1750G>A)   |
| 56 | No | MYBPC3:P p.Trp792Valfs*41(c.2373insG); MYH7:P p.Arg694Cys(c.2080C>T)                                    |
| 57 | No | MYBPC3:P p.Trp792Valfs*41(c.2373insG); MYH7:P p.Arg694Cys(c.2080C>T)                                    |
| 58 | No | MYBPC3:LP p.Arg810Leu(c.2429G>T); TNNI3:P p.Arg162Gln(c.485G>A)   |
| 59 | No | MYBPC3:P p.Phe305Profs*27(c.913_914del); MYH7:LP p.Asn1664Lys(c.4992C>A)                                |
| 60 | No | MYBPC3: Pp.Leu1221Argfs*16(c.3662_3662del); MYH7:LP p.His1524Arg(c.4571A>G)                             |
| 61 | No | MYBPC3: Pc.927-9G>A; MYBPC3:P c.927-9G>A  |
| 62 | No | MYBPC3:LPp.Val388Met(c.1012G>A); MYH7:LP p.Val338Met(c.1012G>A)   |
| 63 | No | MYBPC3:P p.Glu60fs*49(c.177_187del); MYBPC3:P p.Glu1096*(c.3288G>A)                                     |
| 64 | No | MYH7:LP p.Arg143Gln(c.428G>A); TNNT2:P p.Trp287*(c.860G>A)  |
| 65 | No | MYL3:P p.Ala57Gly(c.170C>G); TNNI3:LP p.Arg145Gln(c.434G>A)   |
| 66 | No | MYBPC3:LP p.Arg810His(c.2429G>A); MYH7:LP p.Arg1712Gln(c.5135G>A)                                       |
| 67 | No | MYBPC3:VUS p.His947Asn(c.2839C>A);MYBPC3:P p.Ala181Cysfs*53(c.540_559del);MYH7:LP p.Arg204His(c.611G>A) |
| 68 | No | MYBPC3:LPp.Pro371Arg(c.1112C>G);MYBPC3:Pp.Lys1065Glufs*12(c.3192dup)                                    |

**Supplemental Table 2** – Clinical Characteristics at Time of First MRI. Patients were considered Prevalent HCM-LVSD if they had a history of LVEF below 50 on an echocardiography.

| <b>Demographics at first MRI</b>          | <b>Total<br/>N = 2,751</b> | <b>HCM without<br/>LVSD<br/>N = 2,590</b> | <b>P value</b><br>HCM without LVSD vs.<br>Incident HCM-LVSD | <b>Incident<br/>HCM-LVSD<br/>N = 105</b> | <b>Prevalent<br/>HCM-LVSD<br/>N = 56</b> | <b>P value</b><br>Incident HCM-LVSD vs.<br>Prevalent HCM-LVSD |
|---|----------------------------|---|---|--|--|---|
| Age at first MRI, mean±SD                 | 46.20±17.90                | 46.2±18.0                                 | 0.955   | 46.1±16.4                                | 45.1±18.6                                | 0.726   |
| Age at Diagnosis with HCM, years, mean±SD | 41.89±18.69                | 42.1±20.4                                 | 0.031   | 35.1±19.0                                | 32.6±18.5                                | 0.069   |
| Sex, male, n(%)                           | 1,786 (64.9)               | 1680 (64.9)                               | 0.941   | 69 (65.7)                                | 37 (66.1)                                | 1.000   |
| Follow-up, years, median [IQR]            | 3.2 [1.1-6.1]              | 3.1 [0.5-7.1]                             | <0.001  | 6.0 [2.8-9.9]                            | 4.14 [2.2-6.5]                           | 0.007   |
| <b>Genetics, n(%)</b>                     |                            |   | 0.254*  |  |  | 0.802*  |
| SARC-*                                    | 849 (40.8)                 | 799 (45.2)                                |   | 30 (37.5)                                | 15 (31.9)                                |   |
| SARC VUS*                                 | 377 (18.1)                 | 185 (10.5)                                |   | 7 (8.8)                                  | 4 (8.5)                                  |   |
| SARC+*                                    | 855 (41.1)                 | 784 (44.3)                                |   | 43 (53.8)                                | 28 (59.6)                                |   |
| <i>No genetic testing</i>                 | <i>670 (24.3)</i>          | <i>822 (31.7)</i>                         |   | <i>25 (23.8)</i>                         | <i>9 (16.1)</i>                          |   |
| <b>MRI data</b>                           |                            |   |   |  |  |   |
| LVEF%, mean±SD                            | 66±10                      | 67±10                                     | <0.001  | 57±14                                    | 51±7                                     | 0.018   |
| LVWT mm, mean±SD                          | 21±265                     | 21±273                                    | 0.654   | 12±6                                     | 13±7                                     | 0.711   |
| LVEDV, ml, mean±SD                        | 148±45                     | 148±44                                    | 0.016   | 160±50                                   | 144±57                                   | 0.105   |
| LGE, n(%) – yes                           | 1695 (70.4)                | 1,579 (69.5)                              | 0.002   | 74 (87.1)                                | 45 (83.3)                                | 0.717   |

\*Percentages and P-values represent patients with genetic testing (n=2081)

**Supplemental Table 3** – Clinical Characteristics at Time of Presentation with HCM-LVSD in Patients with and Without Prior Septal Reduction Therapy (excluding 13 patients who underwent SRT after developing HCM-LVSD)

| <b>Demographics at HCM-LVSD presentation</b>     | <b>Total<br/>N = 540</b> | <b>HCM-LVSD Patients<br/>without prior SRT<br/>N = 402</b> | <b>HCM-LVSD Patients<br/>with prior SRT<br/>n = 138</b> | <b>P-value</b> |
|--|--------------------------|--|---|----------------|
| Sex male   | 341 (63.1)               | 257 (63.9)   | 84 (61.0)   | 0.589          |
| Age at developing HCM-LVSD, years, mean (SD)     | 50.5±17.9                | 50.4±18.3  | 51.0±16.8   | 0.708          |
| <b>Genetics, n(%)</b>                            |                          |  |   | 0.191          |
| SARC-*   | 120 (31.3)               | 80 (29.0)  | 40 (37.0)   |                |
| SARC VUS*  | 28 (7.3)                 | 23 (8.3)   | 5 (4.6)   |                |
| SARC+*   | 236 (61.5)               | 173 (62.7)   | 63 (58.3)   |                |
| <i>No genetic testing</i>                        | <i>156 (28.8)</i>        | <i>126 (31.3)</i>  | <i>30 (21.7)</i>  | <i>0.032</i>   |
| NYHA III/IV at presentation with HCM-LVSD, n (%) | 155 (30.7)               | 100 (26.3)   | 55 (44.0)   | <0.001         |
| <b>Echo measures at HCM-LVSD presentation</b>    |                          |  |   |                |
| Maximal LVWT, mm                                 | 17±6                     | 17±5   | 17±6  | 0.749          |
| LVEF%, mean±SD                                   | 40±8                     | 39±8   | 41±7  | 0.032          |
| LVEF<35%, n (%)                                  | 139 (25.7)               | 118 (29.4)   | 21 (15.2)   | 0.044          |
| Obstruction, LVOT > 30 mmHg, n (%)               | 34 (9.5%)                | 21 (8.0)   | 13 (13.8)   | 0.248          |
| LVIDd, mm, mean±SD                               | 50±9                     | 50±9   | 49±9  | 0.701          |
| Left Atrial diameter, mm, mean±SD                | 49±1                     | 48±1   | 52±1  | 0.005          |

\*Percentages and P-values represent patients with genetic testing

**Supplemental Table 4** – Comparison of Events in HCM-LVSD patients With and Without SRT before Developing HCM-LVSD and at Any Time (excluding 13 patients who underwent SRT after developing HCM-LVSD)

| <b>Events</b>                                   | <b>Total<br/>N = 540</b> | <b>HCM-LVSD without<br/>prior SRT<br/>N = 402</b> | <b>HCM-LVSD with<br/>prior SRT<br/>n = 138</b> | <b>P-value</b> |
|---|--------------------------|---|--|----------------|
| <b>Events before developing HCM-LVSD, n (%)</b> |                          |   |  |                |
| ICD implanted                                   | 213 (39.4)               | 147 (36.6)  | 66 (47.8)                                      | 0.025          |
| Appropriate ICD firing                          | 40 (18.8)                | 32 (21.7)   | 8 (12.1)                                       | 0.095          |
| Atrial fibrillation                             | 219 (41.8)               | 161 (41.7)  | 58 (42.0)                                      | 0.696          |
| Stroke  | 19 (5.9)                 | 15 (6.2)  | 4 (4.8)  | 0.818          |
| <b>Events at Any Time, n (%)</b>                |                          |   |  |                |
| ICD implanted                                   | 293 (54.3)               | 207 (51.5)  | 86 (62.3)                                      | 0.035          |
| Appropriate ICD firing                          | 73 (24.9)                | 59 (28.5)   | 14 (16.3)                                      | 0.029          |
| Atrial fibrillation                             | 258 (49.2)               | 187 (48.4)  | 71 (51.4)                                      | 0.612          |
| Stroke  | 27 (8.3)                 | 22 (9.2)  | 5 (6.0)  | 0.491          |
| LVEF<35%  | 181 (34.0)               | 144 (36.5)  | 37 (26.8)                                      | 0.051          |
| Death   | 133 (24.6)               | 99 (24.6)   | 34 (24.6)                                      | 1.000          |
| Transplant                                      | 64 (11.9)                | 48 (11.9)   | 16 (11.6)                                      | 1.000          |
| LVAD  | 10 (2.8)                 | 8 (2.9)   | 2 (2.2)  | 1.000          |