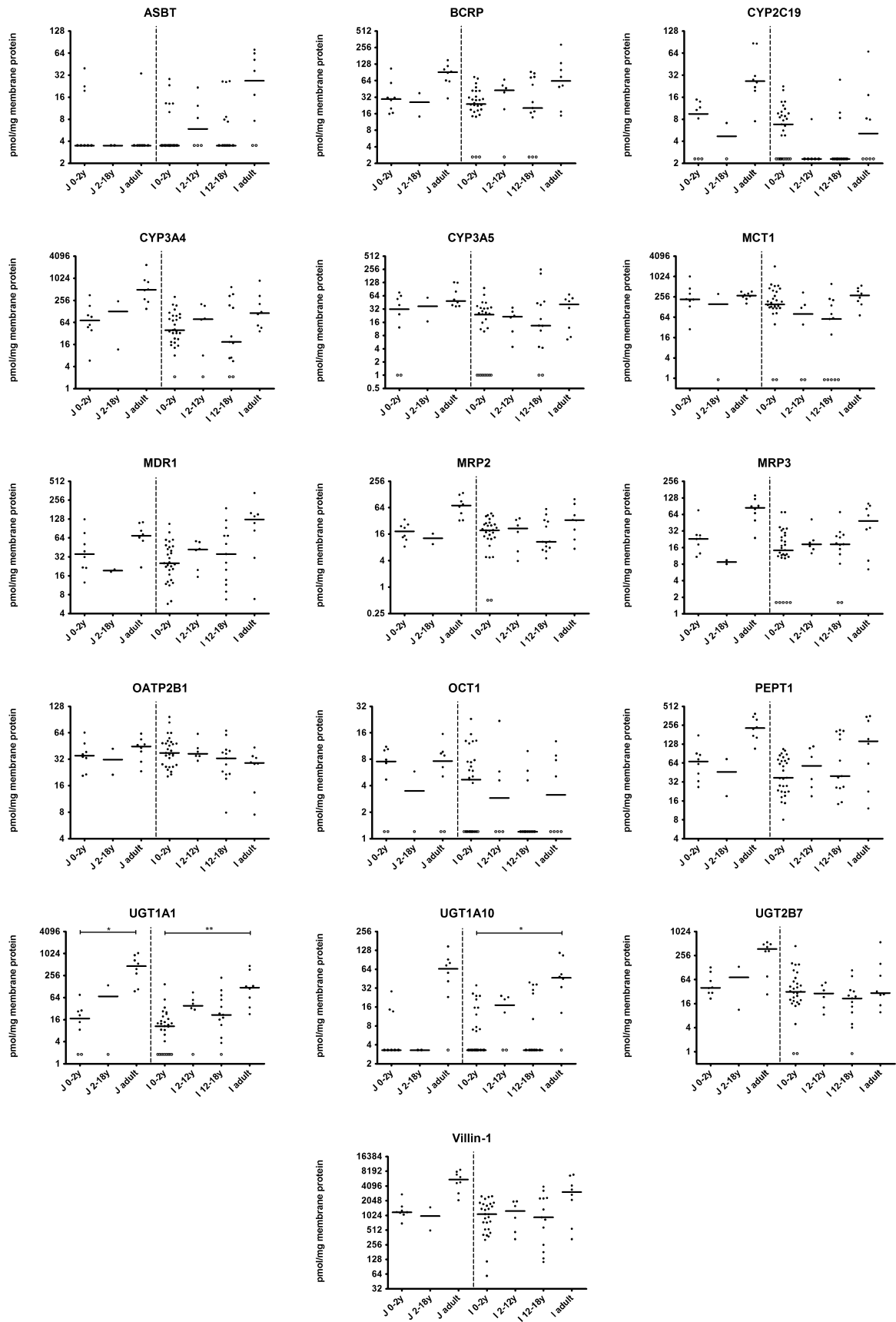


## SUPPLEMENTAL INFORMATION

Drug Metabolism and Disposition

# Ontogeny of Small Intestinal Drug Transporters and Metabolizing Enzymes Based on Targeted Protein Quantification

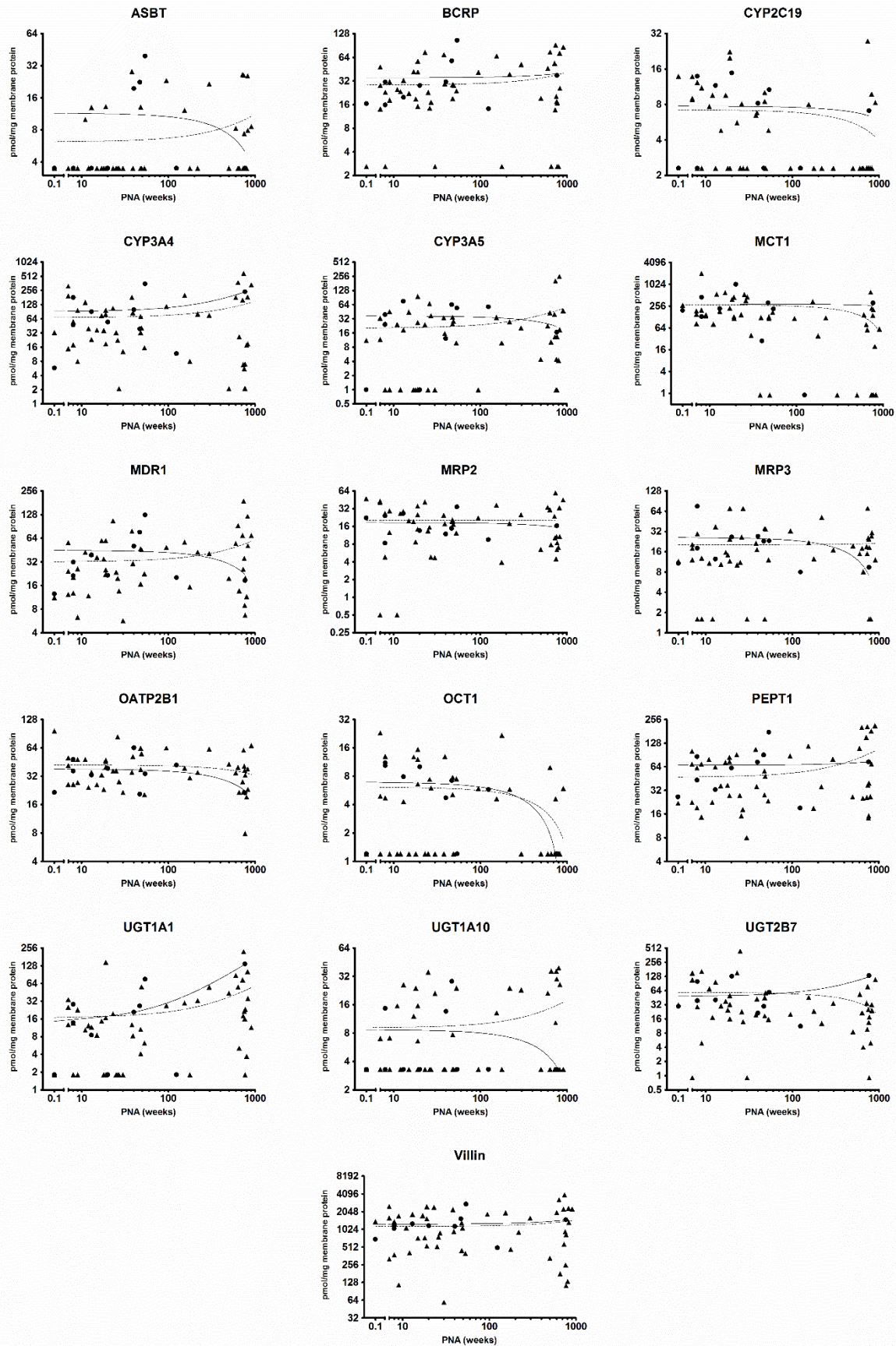
Márton Kiss\*, Richard Mbasu\*, Johan Nicolaï, Karin Barnouin, Apoorva Kotian, Miriam G. Mooij, Nico Kist, Rene M. H. Wijnen, Anna-Lena Ungell, Paul Cutler, Frans G. M. Russel, Saskia N. de Wildt



Supplemental figure 1. Protein abundances of SLC transporters, CYP and UGT enzymes in

the jejunum and ileum of pediatric and adult patients compared among age groups. Data is expressed as pmol/mg membrane protein. Bars represent medians; empty symbols represent imputed values. Adjusted significance: \* $p < 0.0033$ , \*\* $p < 0.00067$ .

Data from 58 pediatric and 16 adult samples are shown in Supplemental figure 1. In jejunum ( $n=18$ ), UGT1A1 showed higher abundances in adulthood versus the 0-2 year pediatric age group. In the ileum ( $n=56$ ), significant increase was noticed between the youngest age group (0-2 year) and adults for UGT1A1 and UGT1A10. Interestingly, ileal and jejunal ASBT could only be detected after 11 and 13 weeks PNA, respectively. Villin-1 abundance was not significantly different between the age groups.



Supplemental figure 2. Protein abundances of SLC transporters, CYP and UGT enzymes in

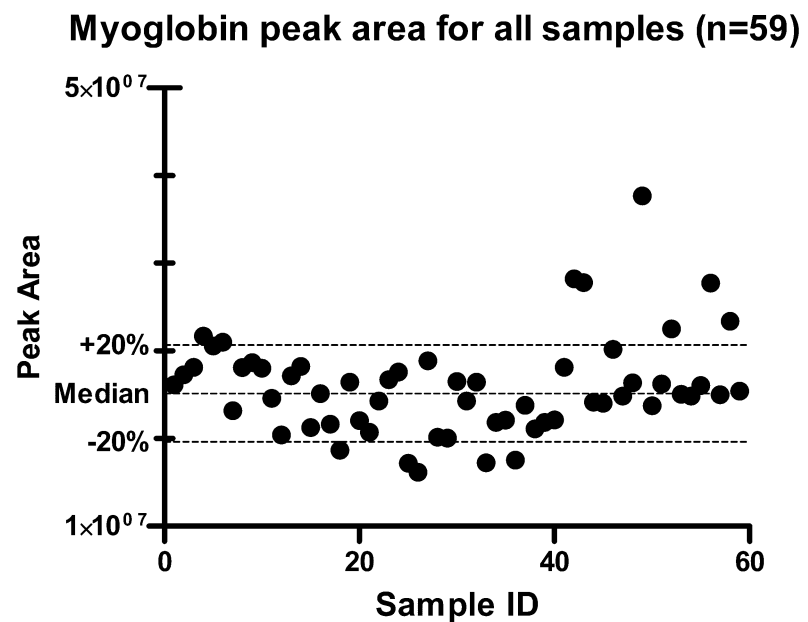
the jejunum and ileum of pediatric patients plotted on a continuous age scale. Data are expressed as pmol/mg membrane protein. Lines are linear regressions fitted to the data. Circles and solid line: jejunal samples; triangles and dotted line: ileal samples.

Without correcting for villin-1, protein abundances showed a significant negative correlation with age for OCT1 and CYP2C19 in the jejunum (n=10), but only without including imputed values. Similarly, to the villin-1 normalized results, examination of the raw data including all imputed values exhibited age-related increase for ASBT and UGT1A1, and negative correlation for MCT1 and CYP2C19 in the ileum (n=48). Using the smaller dataset (with the imputed values excluded) UGT1A10 abundance was higher, while MCT1 and UGT2B7 was lower with age.

| Sample ID | Age       | BCRP | MRP2 | MCT    | MRP3 | ASBT | OATP2B1 | MDR1  | PEPT1 | OCT1 | UGT1A1 | UGT1A10 | CYP2C19 | UGT2B7 | CYP3A4 | CYP3A5 | VIL1 |
|-----------|-----------|------|------|--------|------|------|---------|-------|-------|------|--------|---------|---------|--------|--------|--------|------|
| 018       | 0-2 years | 0.1  | 47.2 | 270.9  | 11.5 | 0.1  | 96.7    | 11.2  | 21.9  | 0.1  | 0.1    | 5.3     | 13.9    | 31.8   | 32.7   | 11.1   | 1384 |
| 012       |           | 14.1 | 0.1  | 83.5   | 12.1 | 0.1  | 26.2    | 12.3  | 22.4  | 0.1  | 12.7   | 7.0     | 8.8     | 0.1    | 14.8   | 11.7   | 321  |
| 021       |           | 28.1 | 40.7 | 152.9  | 17.9 | 0.1  | 41.6    | 24.3  | 68.8  | 4.9  | 34.0   | 3.9     | 13.8    | 108.2  | 195.5  | 33.1   | 1604 |
| 027       |           | 48.2 | 42.9 | 187.8  | 20.5 | 0.1  | 50.2    | 56.0  | 100.5 | 23.0 | 25.3   | 0.1     | 9.0     | 150.5  | 316.7  | 32.7   | 2510 |
| 045       |           | 0.1  | 4.8  | 2030.7 | 0.1  | 0.1  | 26.2    | 12.8  | 19.2  | 4.7  | 0.1    | 0.1     | 0.1     | 28.9   | 17.9   | 0.1    | 377  |
| 047       |           | 23.0 | 26.6 | 201.1  | 29.6 | 0.1  | 48.6    | 20.4  | 61.9  | 13.0 | 13.7   | 0.1     | 12.3    | 40.6   | 55.4   | 25.6   | 1386 |
| 020       |           | 31.4 | 29.2 | 146.8  | 12.9 | 0.1  | 48.2    | 26.1  | 69.2  | 0.1  | 22.8   | 7.1     | 11.1    | 162.6  | 96.2   | 45.5   | 1728 |
| 016       |           | 18.3 | 12.6 | 136.6  | 0.1  | 0.1  | 27.5    | 6.3   | 14.7  | 0.1  | 0.1    | 3.0     | 0.1     | 4.9    | 8.0    | 0.1    | 116  |
| 028       |           | 25.0 | 0.1  | 80.8   | 10.8 | 10.0 | 48.2    | 42.4  | 79.0  | 0.1  | 10.3   | 15.6    | 7.7     | 70.0   | 143.2  | 24.3   | 1082 |
| 010       |           | 23.4 | 26.4 | 543.0  | 0.1  | 0.1  | 24.3    | 11.8  | 22.5  | 0.1  | 12.3   | 0.1     | 9.6     | 17.2   | 39.3   | 0.1    | 407  |
| 042       |           | 32.7 | 28.3 | 183.6  | 37.5 | 13.0 | 35.2    | 39.9  | 63.5  | 4.3  | 11.6   | 26.1    | 0.1     | 96.6   | 23.2   | 18.7   | 1839 |
| 005       |           | 22.3 | 19.9 | 592.3  | 10.4 | 4.5  | 26.0    | 36.5  | 36.6  | 0.1  | 8.5    | 0.1     | 4.8     | 30.1   | 36.8   | 44.4   | 727  |
| 011       |           | 42.0 | 19.2 | 224.4  | 15.6 | 6.4  | 33.0    | 59.5  | 72.3  | 12.8 | 14.7   | 12.1    | 9.6     | 37.7   | 74.9   | 0.1    | 1756 |
| 009       |           | 18.9 | 8.7  | 391.6  | 14.3 | 6.2  | 23.0    | 34.8  | 37.2  | 0.1  | 0.1    | 24.0    | 0.1     | 24.9   | 36.2   | 0.1    | 734  |
| 001       |           | 57.3 | 35.3 | 449.7  | 70.2 | 0.1  | 47.4    | 25.3  | 74.2  | 15.4 | 146.7  | 0.1     | 22.4    | 32.6   | 79.5   | 26.5   | 2495 |
| 026       |           | 41.7 | 25.2 | 130.8  | 24.6 | 13.2 | 45.7    | 59.7  | 84.7  | 6.6  | 16.7   | 6.6     | 19.9    | 50.2   | 97.7   | 95.8   | 1547 |
| 054       |           | 15.2 | 14.3 | 118.8  | 11.6 | 0.1  | 39.9    | 22.2  | 27.4  | 12.1 | 0.1    | 15.6    | 0.1     | 16.0   | 18.7   | 0.1    | 532  |
| 022       |           | 74.3 | 41.6 | 148.7  | 10.2 | 0.1  | 36.3    | 106.8 | 91.2  | 0.1  | 19.5   | 0.1     | 5.6     | 152.2  | 107.5  | 24.0   | 2423 |
| 043       |           | 22.9 | 13.4 | 533.2  | 11.1 | 6.3  | 36.6    | 23.6  | 27.6  | 0.1  | 0.1    | 35.4    | 0.1     | 438.7  | 32.5   | 0.1    | 525  |
| 050       |           | 14.4 | 15.4 | 361.7  | 26.5 | 5.1  | 83.6    | 19.7  | 15.2  | 7.4  | 0.1    | 0.1     | 8.1     | 22.7   | 22.3   | 67.2   | 762  |
| 008       |           | 17.2 | 4.8  | 456.8  | 70.2 | 0.1  | 28.0    | 13.6  | 18.3  | 6.0  | 0.1    | 0.1     | 0.1     | 13.9   | 0.1    | 37.2   | 884  |
| 046       |           | 0.1  | 4.7  | 39.4   | 0.1  | 0.1  | 21.5    | 5.7   | 8.0   | 0.1  | 0.1    | 21.1    | 0.1     | 0.1    | 13.0   | 0.1    | 59   |
| 030       |           | 69.7 | 24.7 | 0.1    | 21.5 | 28.3 | 35.2    | 78.5  | 106.6 | 0.1  | 12.7   | 0.1     | 6.5     | 19.4   | 184.0  | 33.7   | 2218 |
| 055       |           | 29.5 | 17.7 | 123.8  | 17.2 | 5.3  | 51.6    | 30.5  | 35.9  | 12.9 | 8.3    | 0.1     | 6.8     | 42.6   | 85.6   | 15.6   | 941  |
| 051       |           | 19.1 | 19.5 | 130.1  | 0.1  | 0.1  | 37.7    | 16.7  | 28.0  | 5.1  | 4.1    | 0.1     | 10.1    | 18.5   | 32.7   | 34.7   | 447  |
| 057       |           | 28.9 | 20.7 | 116.6  | 35.4 | 13.1 | 63.6    | 47.0  | 56.7  | 7.8  | 10.6   | 7.7     | 8.5     | 45.1   | 71.8   | 25.0   | 1316 |
| 029       |           | 28.4 | 17.3 | 0.1    | 34.9 | 6.6  | 55.6    | 45.6  | 48.5  | 0.1  | 56.3   | 0.1     | 0.1     | 57.0   | 40.9   | 28.6   | 1080 |
| 052       |           | 23.9 | 12.4 | 171.6  | 12.1 | 4.2  | 20.4    | 22.6  | 23.4  | 7.5  | 6.2    | 24.0    | 4.8     | 15.6   | 15.4   | 9.9    | 398  |

|     |             |      |      |       |      |      |      |       |       |      |       |      |      |       |       |       |      |
|-----|-------------|------|------|-------|------|------|------|-------|-------|------|-------|------|------|-------|-------|-------|------|
| 056 | 2-12 years  | 41.3 | 22.2 | 116.8 | 32.7 | 23.2 | 63.7 | 48.8  | 87.7  | 5.9  | 26.9  | 0.1  | 0.1  | 19.9  | 116.9 | 0.1   | 1850 |
| 053 |             | 66.6 | 36.6 | 343.4 | 21.6 | 12.2 | 39.0 | 56.8  | 117.7 | 4.6  | 29.8  | 13.1 | 8.0  | 45.5  | 200.6 | 34.3  | 1957 |
| 048 |             | 0.1  | 3.9  | 38.9  | 12.6 | 2.3  | 30.7 | 15.3  | 18.9  | 21.8 | 0.1   | 0.1  | 0.1  | 23.4  | 8.0   | 9.9   | 465  |
| 024 |             | 39.1 | 17.9 | 120.8 | 51.9 | 6.8  | 34.9 | 42.6  | 35.4  | 5.8  | 32.7  | 24.0 | 0.1  | 12.8  | 80.9  | 27.7  | 913  |
| 044 |             | 52.1 | 25.2 | 0.1   | 17.0 | 21.6 | 62.2 | 40.9  | 80.0  | 1.8  | 55.2  | 22.9 | 0.1  | 34.2  | 75.9  | 20.5  | 1584 |
| 013 |             | 19.3 | 6.5  | 0.1   | 19.6 | 0.1  | 42.8 | 19.7  | 26.4  | 0.1  | 43.6  | 0.1  | 0.1  | 8.5   | 0.1   | 4.4   | 333  |
| 023 |             | 46.5 | 33.6 | 147.2 | 14.9 | 8.3  | 34.8 | 54.7  | 109.9 | 0.1  | 88.1  | 21.2 | 0.1  | 53.5  | 180.7 | 22.5  | 1971 |
| 058 |             | 74.7 | 30.8 | 79.5  | 17.9 | 0.1  | 39.7 | 92.5  | 203.0 | 9.9  | 55.8  | 0.1  | 0.1  | 21.6  | 376.6 | 43.3  | 3254 |
| 014 | 12-18 years | 0.1  | 7.8  | 56.7  | 8.1  | 0.1  | 21.5 | 13.7  | 25.4  | 0.1  | 5.1   | 36.5 | 0.1  | 4.0   | 26.5  | 10.3  | 180  |
| 002 |             | 53.9 | 23.7 | 616.2 | 19.1 | 26.4 | 27.9 | 69.3  | 151.7 | 0.1  | 73.9  | 0.1  | 0.1  | 34.6  | 159.7 | 39.7  | 2260 |
| 033 |             | 13.7 | 10.2 | 0.1   | 15.0 | 4.5  | 21.8 | 25.8  | 26.0  | 0.1  | 18.1  | 0.1  | 0.1  | 9.6   | 6.8   | 13.3  | 575  |
| 017 |             | 92.1 | 59.5 | 222.0 | 70.7 | 26.1 | 60.5 | 190.2 | 207.0 | 4.6  | 222.5 | 10.3 | 27.7 | 77.7  | 587.8 | 203.6 | 3944 |
| 006 |             | 20.3 | 4.5  | 0.1   | 25.7 | 7.4  | 41.0 | 35.5  | 37.5  | 0.1  | 21.6  | 36.3 | 0.1  | 25.4  | 5.6   | 0.1   | 931  |
| 037 |             | 17.6 | 10.7 | 141.9 | 24.4 | 0.1  | 36.9 | 8.9   | 14.2  | 0.1  | 16.1  | 29.9 | 0.1  | 13.4  | 0.1   | 4.4   | 254  |
| 040 |             | 0.1  | 6.5  | 204.2 | 0.1  | 0.1  | 7.9  | 6.7   | 15.2  | 0.1  | 0.1   | 0.1  | 0.1  | 0.1   | 7.0   | 0.1   | 113  |
| 041 |             | 16.7 | 8.4  | 0.1   | 18.4 | 0.1  | 32.8 | 19.9  | 39.6  | 0.1  | 23.3  | 0.1  | 0.1  | 17.5  | 0.1   | 13.4  | 835  |
| 019 |             | 0.1  | 7.0  | 19.6  | 0.1  | 0.1  | 19.2 | 11.5  | 26.7  | 0.1  | 3.7   | 39.3 | 0.1  | 4.9   | 17.7  | 4.2   | 134  |
| 038 |             | 72.8 | 33.2 | 0.1   | 27.2 | 25.7 | 38.1 | 121.7 | 182.3 | 0.1  | 101.5 | 0.1  | 9.8  | 32.2  | 186.4 | 254.1 | 2323 |
| 007 |             | 25.9 | 10.8 | 0.1   | 30.7 | 7.9  | 23.2 | 51.3  | 69.6  | 1.5  | 35.6  | 26.2 | 0.1  | 24.0  | 18.7  | 18.9  | 1342 |
| 049 |             | 86.7 | 44.9 | 59.8  | 12.1 | 8.6  | 67.6 | 69.1  | 213.5 | 5.9  | 11.4  | 0.1  | 8.3  | 108.9 | 336.5 | 47.6  | 2263 |

Supplemental figure 3. Heatmap of protein abundances of SLC transporters, CYP and UGT enzymes in the ileum of pediatric patients. Blue represents low, white medium and red high abundance. Samples are sorted by increasing PNA.



Supplemental figure 4. Figure represents peak area for myoglobin across all the samples analyzed on different days. Overall, the peak area for majority of the samples are well within  $\pm 20\%$  of the median value (except for few outliers). The relative standard deviation of myoglobin peak area (RSD) across all the samples is 19.8% (calculation not shown) which is acceptable for a protein based LCMS assay.



| Protein        | Peptide               | Mass   | Ion/z | LLOQ (pmoles) | Q1     | Q3      |
|----------------|-----------------------|--------|-------|---------------|--------|---------|
| <b>BCRP</b>    | SSLLDVLAAR            | 1044.2 | 2Y6   | 0.01          | 522.81 | 644.37  |
|                | SSLLDVLAAR*           | 1054.2 |       |               | 527.81 | 654.38  |
| <b>MRP2</b>    | VLGPNGLLK             | 910.1  | 2Y7   | 0.002         | 455.79 | 698.42  |
|                | VLGPNGLLK*            | 918.1  |       |               | 459.80 | 706.43  |
| <b>MCT</b>     | SITVFFK               | 841.0  | 2Y5   | 0.004         | 421.25 | 641.37  |
|                | SITVFFK*              | 849.0  |       |               | 425.25 | 649.38  |
| <b>MRP3</b>    | IDGLNVADIGLH<br>DLR   | 1620.8 | 3Y9   | 0.004         | 540.96 | 1009.54 |
|                | IDGLNVADIGLH<br>DLR*  | 1630.8 |       |               | 544.30 | 1019.55 |
| <b>ASBT</b>    | ENGTEPESSFYK          | 1387.4 | 2Y5   | 0.01          | 694.30 | 631.31  |
|                | ENGTEPESSFYK<br>*     | 1395.4 |       |               | 698.31 | 639.32  |
| <b>OATP2B1</b> | VLLQTLR               | 842.0  | 2Y6   | 0.002         | 421.78 | 743.48  |
|                | VLLQTLR*              | 852.1  |       |               | 426.78 | 753.49  |
| <b>MDR1</b>    | NTTGALTTR             | 934.0  | 2Y7   | 0.004         | 467.75 | 719.41  |
|                | NTTGALTTR*            | 944.0  |       |               | 472.76 | 729.41  |
| <b>PEPT1</b>   | TLPVFPK               | 801.0  | 2Y5   | 0.004         | 401.25 | 587.36  |
|                | TLPVFPK*              | 809.0  |       |               | 405.25 | 595.37  |
| <b>OCT1</b>    | LSPSFADLFR            | 1152.3 | 2Y7   | 0.004         | 576.81 | 855.44  |
|                | LSPSFADLFR*           | 1162.3 |       |               | 581.81 | 865.44  |
| <b>UGT1A1</b>  | GHEIVVLAPDAS<br>LYIR  | 1753.0 | 3Y8   | 0.004         | 584.99 | 934.50  |
|                | GHEIVVLAPDAS<br>LYIR* | 1763.0 |       |               | 588.33 | 944.51  |
| <b>UGT1A10</b> | YFSLPSVVFTR           | 1315.5 | 2Y7   | 0.01          | 658.36 | 805.46  |
|                | YFSLPSVVFTR*          | 1325.5 |       |               | 663.36 | 815.47  |
| <b>CYP2C19</b> | GHFPLAER              | 926.1  | 2Y6   | 0.01          | 463.75 | 732.40  |
|                | GHFPLAER*             | 936.1  |       |               | 468.75 | 742.41  |
| <b>UGT2B7</b>  | ADVWLIR               | 872.0  | 2Y5   | 0.004         | 436.75 | 686.44  |
|                | ADVWLIR*              | 882.0  |       |               | 441.76 | 696.44  |
| <b>CYP3A4</b>  | EVTNFLR               | 878.0  | 2Y5   | 0.001         | 439.74 | 650.36  |
|                | EVTNFLR*              | 888.0  |       |               | 444.74 | 660.37  |

|               |            |        |     |       |        |        |
|---------------|------------|--------|-----|-------|--------|--------|
| <b>CYP3A5</b> | DTINFLSK   | 937.1  | 2Y6 | 0.004 | 469.25 | 721.42 |
|               | DTINFLSK*  | 945.1  |     |       | 473.26 | 729.44 |
| <b>VILLIN</b> | GDVFLDLGK  | 1076.3 | 2Y6 | 0.002 | 538.80 | 658.41 |
|               | GDVFLDLGK* | 1084.3 |     |       | 542.81 | 666.43 |

Supplemental table 1. Multiple reaction monitoring (MRM) transitions of the representative and their corresponding SIL peptides (Bold\*) for each protein. Each selected peptide was unique to the protein of interest and followed the in-silico peptide criteria defined by Kamiie et al. (2008).

Lower limit of quantitation (LLOQ) was determined by a linearity check of each peptide

|         | BCRP | MRP2 | MCT1 | MRP3 | ASBT | OATP2B1 | MDR1 | PEPT1 | OCT1 | UGT1A1 | UGT1A10 | CYP2C19 | UGT2B7 | CYP3A4 | CYP3A5 | VIL1 |
|---------|------|------|------|------|------|---------|------|-------|------|--------|---------|---------|--------|--------|--------|------|
| BCRP    |      | 0.74 |      | 0.47 | 0.59 | 0.45    | 0.88 | 0.90  |      | 0.71   |         | 0.36    | 0.63   | 0.83   | 0.57   | 0.87 |
| MRP2    |      |      |      |      | 0.32 | 0.53    | 0.57 | 0.67  |      | 0.49   |         | 0.58    | 0.63   | 0.78   | 0.55   | 0.79 |
| MCT1    |      |      |      |      |      |         |      |       |      |        |         |         |        |        |        |      |
| MRP3    |      |      |      |      | 0.42 | 0.47    | 0.48 | 0.40  | 0.34 | 0.57   |         |         |        |        | 0.45   | 0.55 |
| ASBT    |      |      |      |      |      | 0.31    | 0.65 | 0.66  |      | 0.43   |         |         | 0.35   | 0.49   | 0.36   | 0.55 |
| OATP2B1 |      |      |      |      |      |         | 0.37 | 0.43  | 0.37 | 0.31   |         | 0.46    | 0.58   | 0.49   | 0.43   | 0.56 |
| MDR1    |      |      |      |      |      |         |      | 0.92  |      | 0.64   |         |         | 0.62   | 0.78   | 0.56   | 0.85 |
| PEPT1   |      |      |      |      |      |         |      |       |      | 0.71   |         | 0.32    | 0.66   | 0.85   | 0.57   | 0.90 |
| OCT1    |      |      |      |      |      |         |      |       |      |        |         | 0.33    |        |        |        | 0.29 |
| UGT1A1  |      |      |      |      |      |         |      |       |      |        |         |         | 0.33   | 0.51   | 0.45   | 0.66 |
| UGT1A10 |      |      |      |      |      |         |      |       |      |        |         | -0.29   |        |        | -0.31  |      |
| CYP2C19 |      |      |      |      |      |         |      |       |      |        |         |         | 0.44   | 0.51   | 0.50   | 0.42 |
| UGT2B7  |      |      |      |      |      |         |      |       |      |        |         |         |        | 0.66   | 0.45   | 0.71 |
| CYP3A4  |      |      |      |      |      |         |      |       |      |        |         |         |        |        | 0.60   | 0.82 |
| CYP3A5  |      |      |      |      |      |         |      |       |      |        |         |         |        |        |        | 0.62 |

Supplemental table 2. Correlation of non-normalized protein abundances of DTs and DMEs with each other in the pediatric ileum. Spearman  $\rho$ -values are shown if  $p < 0.05$  ( $n=48$ ). Villin-1 concentrations correlated positively with most of the proteins in our analysis ( $p < 0.05$ ). The only protein that correlated negatively with other proteins was UGT1A10 (with CYP2C19 and CYP3A5). Finally, no correlation was observed between MCT1 and other proteins analyzed in the current study.

| ASBT           | Raw abundance (pmol/mg membrane protein) |                |                |               |                |                 |                | Villin-1 corrected ratios |                |                |               |                |                 |                |
|----------------|------------------------------------------|----------------|----------------|---------------|----------------|-----------------|----------------|---------------------------|----------------|----------------|---------------|----------------|-----------------|----------------|
|                | J 0-2y                                   | J 2-18y        | J Adult        | I 0-2y        | I 2-12y        | I 12-18z        | I Adult        | J 0-2y                    | J 2-18y        | J Adult        | I 0-2y        | I 2-12y        | I 12-18y        | I Adult        |
| Min            | 3.5                                      | 3.5            | 3.5            | 3.5           | 3.5            | 3.5             | 3.5            | -8.507                    | -8.737         | -11.29         | -9.490        | -8.031         | -9.865          | -10.89         |
| Min (detected) | 19.5                                     | -              | 33.6           | 10.0          | 8.3            | 7.4             | 7.6            | -6.119                    | -              | -6.422         | -7.145        | -7.892         | -8.038          | -6.936         |
| <b>Median</b>  | 3.5                                      | 3.5            | 3.5            | 3.5           | 5.9            | 3.5             | 26.9           | -7.942                    | -7.949         | -10.62         | -7.251        | -7.194         | -6.976          | -6.452         |
| Max            | 39.5                                     | 3.5            | 33.6           | 28.3          | 21.6           | 26.4            | 71.0           | -5.886                    | -7.161         | -6.422         | -4.081        | -6.198         | -5.019          | -5.760         |
| Mean           | 12.4                                     | 3.5            | 7.3            | 6.3           | 8.8            | 9.7             | 31.8           | -7.416                    | -7.949         | -10.09         | -7.503        | -7.181         | -6.913          | -6.932         |
| SD             | 13.5                                     | 0.0            | 10.6           | 6.3           | 7.2            | 9.5             | 27.7           | 1.173                     | 1.114          | 1.616          | 1.291         | 0.720          | 1.300           | 1.638          |
| CV%            | 109.4                                    | 0.0            | 146.5          | 100.4         | 82.2           | 97.5            | 87.0           | 15.8                      | 14.0           | 16.0           | 17.2          | 10.0           | 18.8            | 23.6           |
| Detected       | 3/8                                      | 0/2            | 1/8            | 6/29          | 3/9            | 6/13            | 6/8            | 3/8                       | 0/2            | 1/8            | 6/29          | 3/9            | 6/13            | 6/8            |
| <b>BCRP</b>    | <b>J 0-2y</b>                            | <b>J 2-18y</b> | <b>J Adult</b> | <b>I 0-2y</b> | <b>I 2-12y</b> | <b>I 12-18y</b> | <b>I Adult</b> | <b>J 0-2y</b>             | <b>J 2-18y</b> | <b>J Adult</b> | <b>I 0-2y</b> | <b>I 2-12y</b> | <b>I 12-18y</b> | <b>I Adult</b> |
| Min            | 15.9                                     | 14.2           | 30.3           | 2.6           | 2.6            | 2.6             | 14.8           | -6.053                    | -5.302         | -6.413         | -9.034        | -7.461         | -6.093          | -6.468         |
| Min (detected) | 15.9                                     | 14.2           | 30.3           | 14.1          | 19.3           | 13.7            | 14.8           | -6.053                    | -5.302         | -6.413         | -5.91         | -5.406         | -5.695          | -6.468         |
| <b>Median</b>  | <b>29.6</b>                              | <b>26.0</b>    | <b>91.1</b>    | <b>23.9</b>   | <b>42.8</b>    | <b>20.3</b>     | <b>63.4</b>    | -5.328                    | -5.220         | -5.909         | -5.277        | -4.902         | -5.421          | -5.036         |
| Max            | 105.7                                    | 37.7           | 150.5          | 74.3          | 66.6           | 92.1            | 288.3          | -4.698                    | -5.137         | -5.539         | -2.666        | -4.107         | -3.851          | -4.487         |
| Mean           | 38.3                                     | 26.0           | 88.7           | 28.2          | 37.7           | 37.1            | 91.1           | -5.344                    | -5.220         | -5.961         | -5.300        | -5.221         | -5.325          | -5.212         |
| SD             | 30.4                                     | 16.6           | 37.0           | 17.7          | 23.2           | 33.9            | 89.1           | 0.499                     | 0.117          | 0.267          | 1.067         | 1.179          | 0.554           | 0.645          |
| CV%            | 79.2                                     | 64.0           | 41.7           | 62.5          | 61.6           | 91.4            | 97.7           | 9.3                       | 2.2            | 4.5            | 20.1          | 22.6           | 10.4            | 12.4           |
| Detected       | 8/8                                      | 2/2            | 8/8            | 26/29         | 5/6            | 10/13           | 8/8            | 8/8                       | 2/2            | 8/8            | 26/29         | 5/6            | 10/13           | 8/8            |
| <b>CYP2C19</b> | <b>J 0-2y</b>                            | <b>J 2-18y</b> | <b>J Adult</b> | <b>I 0-2y</b> | <b>I 2-12y</b> | <b>I 12-18y</b> | <b>I Adult</b> | <b>J 0-2y</b>             | <b>J 2-18y</b> | <b>J Adult</b> | <b>I 0-2y</b> | <b>I 2-12y</b> | <b>I 12-18y</b> | <b>I Adult</b> |
| Min            | 2.3                                      | 2.3            | 7.5            | 2.3           | 2.3            | 2.3             | 2.3            | -9.373                    | -7.737         | -8.590         | -9.627        | -9.718         | -10.44          | -10.52         |
| Min (detected) | 8.2                                      | 7.1            | 7.5            | 4.8           | 8.0            | 8.3             | 7.9            | -8.004                    | -7.709         | -8.590         | -8.747        | -7.935         | -8.085          | -9.043         |
| <b>Median</b>  | <b>9.5</b>                               | <b>4.7</b>     | <b>26.6</b>    | <b>6.8</b>    | <b>2.3</b>     | <b>2.3</b>      | <b>5.1</b>     | -7.568                    | -7.723         | -7.653         | -7.255        | -8.271         | -7.942          | -8.333         |
| Max            | 14.8                                     | 7.1            | 86.6           | 22.4          | 8.0            | 27.7            | 66.9           | -6.321                    | -7.709         | -6.537         | -4.657        | -7.152         | -5.595          | -6.630         |
| Mean           | 8.3                                      | 4.7            | 38.2           | 7.5           | 3.3            | 5.3             | 13.7           | -7.634                    | -7.723         | -7.432         | -7.222        | -8.409         | -7.858          | -8.503         |
| SD             | 5.3                                      | 3.4            | 30.5           | 5.4           | 2.3            | 7.2             | 22.1           | 1.139                     | 0.020          | 0.718          | 1.268         | 1.014          | 1.503           | 1.371          |
| CV%            | 64.4                                     | 72.2           | 79.7           | 71.8          | 71.6           | 135.9           | 161.9          | 14.9                      | 0.3            | 9.7            | 17.6          | 12.1           | 19.1            | 16.1           |
| Detected       | 5/8                                      | 1/2            | 8/8            | 19/29         | 1/6            | 3/13            | 4/8            | 5/8                       | 1/2            | 8/8            | 19/29         | 1/6            | 3/13            | 4/8            |

| CYP3A4         | J 0-2y       | J 2-18y      | J Adult      | I 0-2y       | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|--------------|--------------|--------------|--------------|-------------|-------------|--------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 5.8          | 11.7         | 149.7        | 2.1          | 2.1         | 2.1         | 36.4         | -6.903 | -5.417  | -4.864  | -8.691 | -7.281  | -8.607   | -5.525  |
| Min (detected) | 5.8          | 11.7         | 149.7        | 8.0          | 8.0         | 5.6         | 36.4         | -6.903 | -5.417  | -4.864  | -6.309 | -5.869  | -7.368   | -5.525  |
| <b>Median</b>  | <b>72.9</b>  | <b>126.9</b> | <b>496.4</b> | <b>39.3</b>  | <b>78.4</b> | <b>18.7</b> | <b>115.4</b> | -4.115 | -4.019  | -3.300  | -4.306 | -3.939  | -3.823   | -4.358  |
| Max            | 353.3        | 242.0        | 2354.0       | 316.7        | 200.6       | 587.8       | 879.2        | -2.720 | -2.621  | -1.402  | -2.187 | -3.286  | -2.746   | -2.656  |
| Mean           | 109.0        | 126.9        | 714.3        | 69.4         | 91.4        | 133.3       | 223.2        | -4.268 | -4.019  | -3.325  | -4.325 | -4.627  | -4.708   | -4.144  |
| SD             | 111.9        | 162.8        | 714.4        | 69.8         | 83.9        | 189.6       | 283.5        | 1.363  | 1.977   | 0.960   | 1.180  | 1.620   | 2.075    | 0.962   |
| CV%            | 102.6        | 128.4        | 100.0        | 100.6        | 91.8        | 142.2       | 127.0        | 31.9   | 49.2    | 28.9    | 27.3   | 35.0    | 44.1     | 23.2    |
| Detected       | 8/8          | 2/2          | 8/8          | 28/29        | 5/6         | 11/13       | 8/8          | 8/8    | 2/2     | 8/8     | 28/29  | 5/6     | 11/13    | 8/8     |
| CYP3A5         | J 0-2y       | J 2-18y      | J Adult      | I 0-2y       | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 1.0          | 16.7         | 36.7         | 1.0          | 4.4         | 1.0         | 6.5          | -10.28 | -6.475  | -7.596  | -10.93 | -6.456  | -9.937   | -8.338  |
| Min (detected) | 12.2         | 16.7         | 36.7         | 9.9          | 4.4         | 4.2         | 6.5          | -6.561 | -6.475  | -7.596  | -6.961 | -6.456  | -6.231   | -8.338  |
| <b>Median</b>  | <b>31.9</b>  | <b>37.2</b>  | <b>48.8</b>  | <b>24.0</b>  | <b>21.5</b> | <b>13.4</b> | <b>40.9</b>  | -5.641 | -4.795  | -6.282  | -5.958 | -6.045  | -5.830   | -6.255  |
| Max            | 75.8         | 57.6         | 129.9        | 95.8         | 34.3        | 254.1       | 68.5         | -4.067 | -3.116  | -5.221  | -3.504 | -5.044  | -3.192   | -4.795  |
| Mean           | 33.4         | 37.2         | 68.4         | 22.6         | 19.9        | 50.4        | 35.7         | -6.382 | -4.795  | -6.391  | -6.477 | -5.903  | -5.724   | -6.455  |
| SD             | 28.8         | 28.9         | 39.6         | 22.2         | 11.1        | 81.5        | 24.4         | 2.310  | 2.375   | 0.824   | 2.037  | 0.534   | 1.617    | 1.019   |
| CV%            | 84.9         | 77.9         | 57.9         | 98.4         | 55.8        | 161.7       | 68.4         | 36.2   | 49.5    | 12.9    | 31.5   | 9.0     | 28.2     | 15.8    |
| Detected       | 6/8          | 2/2          | 8/8          | 20/29        | 6/6         | 11/13       | 8/8          | 6/8    | 2/2     | 8/8     | 20/29  | 6/6     | 11/13    | 8/8     |
| MCT1           | J 0-2y       | J 2-18y      | J Adult      | I 0-2y       | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 28.2         | 0.9          | 161.4        | 0.9          | 0.9         | 0.9         | 72.4         | -5.354 | -9.198  | -5.625  | -11.35 | -10.86  | -11.42   | -5.500  |
| Min (detected) | 28.2         | 311.6        | 161.4        | 39.4         | 38.9        | 19.6        | 72.4         | -5.354 | -2.256  | -5.625  | -4.027 | -3.742  | -5.356   | -5.500  |
| <b>Median</b>  | <b>215.8</b> | <b>156.3</b> | <b>279.2</b> | <b>152.9</b> | <b>79.9</b> | <b>56.7</b> | <b>281.6</b> | -2.420 | -5.727  | -4.268  | -2.472 | -3.661  | -5.242   | -3.468  |
| Max            | 1023.0       | 311.6        | 365.1        | 2031.0       | 343.4       | 616.2       | 546.7        | -0.208 | -2.256  | -3.024  | 2.429  | -2.511  | 0.852    | 0.719   |
| Mean           | 322.0        | 156.3        | 280.9        | 280.2        | 108.7       | 108.0       | 295.5        | -2.540 | -5.727  | -4.207  | -2.614 | -5.371  | -5.579   | -3.169  |
| SD             | 308.9        | 219.7        | 69.9         | 374.5        | 130.3       | 171.4       | 161.2        | 1.573  | 4.909   | 0.830   | 2.781  | 3.486   | 4.248    | 1.815   |
| CV%            | 95.9         | 140.6        | 24.9         | 133.6        | 119.8       | 158.7       | 54.5         | 62.0   | 85.7    | 19.7    | 106.4  | 64.9    | 76.1     | 57.3    |
| Detected       | 8/8          | 1/2          | 8/8          | 27/29        | 4/6         | 8/13        | 8/8          | 8/8    | 1/2     | 8/8     | 27/29  | 4/6     | 8/13     | 8/8     |

| MDR1           | J 0-2y      | J 2-18y     | J Adult     | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|-------------|-------------|-------------|-------------|-------------|-------------|--------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 12.5        | 18.5        | 21.7        | 5.7         | 15.3        | 6.7         | 6.8          | -5.810 | -6.334  | -7.048  | -6.944 | -5.274  | -5.387   | -6.306  |
| Min (detected) | 12.5        | 18.5        | 21.7        | 5.7         | 15.3        | 6.7         | 6.8          | -5.810 | -6.334  | -7.048  | -6.944 | -5.274  | -5.387   | -6.306  |
| <b>Median</b>  | <b>35.4</b> | <b>19.3</b> | <b>69.5</b> | <b>25.3</b> | <b>41.8</b> | <b>35.5</b> | <b>125.6</b> | -5.042 | -5.483  | -6.312  | -4.820 | -5.014  | -4.710   | -4.444  |
| Max            | 126.7       | 20.1        | 113.9       | 106.8       | 56.8        | 190.2       | 331.6        | -4.344 | -4.632  | -4.701  | -3.380 | -4.076  | -3.537   | -4.134  |
| Mean           | 47.5        | 19.3        | 73.8        | 33.1        | 38.3        | 55.1        | 126.8        | -5.095 | -5.483  | -6.231  | -5.039 | -4.829  | -4.560   | -4.771  |
| SD             | 37.8        | 1.1         | 29.7        | 23.1        | 17.4        | 54.1        | 99.6         | 0.635  | 1.203   | 0.687   | 0.794  | 0.477   | 0.555    | 0.776   |
| CV%            | 79.7        | 5.9         | 40.3        | 69.7        | 45.4        | 98.1        | 78.6         | 12.5   | 22.0    | 11.0    | 15.8   | 9.9     | 12.2     | 16.3    |
| Detected       | 8/8         | 2/2         | 8/8         | 29/29       | 6/6         | 13/13       | 8/8          | 8/8    | 2/2     | 8/8     | 29/29  | 6/6     | 13/13    | 8/8     |
| MRP2           | J 0-2y      | J 2-18y     | J Adult     | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 8.3         | 9.5         | 32.8        | 0.5         | 3.9         | 4.5         | 7.4          | -7.000 | -6.503  | -6.712  | -11.20 | -6.890  | -7.679   | -6.953  |
| Min (detected) | 8.3         | 9.5         | 32.8        | 4.7         | 3.9         | 4.5         | 7.4          | -7.000 | -6.503  | -6.712  | -7.519 | -6.890  | -7.679   | -6.953  |
| <b>Median</b>  | <b>18.5</b> | <b>13.0</b> | <b>71.5</b> | <b>19.5</b> | <b>21.6</b> | <b>10.7</b> | <b>33.3</b>  | -6.384 | -6.109  | -6.289  | -5.871 | -5.808  | -6.050   | -6.306  |
| Max            | 34.3        | 16.4        | 137.6       | 47.2        | 36.6        | 59.5        | 99.4         | -4.972 | -5.714  | -5.636  | -3.206 | -5.670  | -4.119   | -4.792  |
| Mean           | 19.5        | 13.0        | 76.0        | 20.6        | 20.6        | 19.9        | 40.8         | -6.158 | -6.109  | -6.233  | -5.903 | -5.971  | -5.823   | -6.232  |
| SD             | 8.8         | 4.9         | 39.6        | 12.7        | 13.7        | 17.4        | 32.2         | 0.692  | 0.558   | 0.443   | 1.540  | 0.466   | 1.139    | 0.672   |
| CV%            | 45.1        | 37.7        | 52.1        | 61.5        | 66.2        | 87.6        | 79.1         | 11.2   | 9.1     | 7.1     | 26.1   | 7.8     | 19.6     | 10.8    |
| Detected       | 8/8         | 2/2         | 8/8         | 27/29       | 6/6         | 13/13       | 8/8          | 8/8    | 2/2     | 8/8     | 27/29  | 6/6     | 13/13    | 8/8     |
| MRP3           | J 0-2y      | J 2-18y     | J Adult     | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 10.8        | 8.0         | 23.9        | 1.6         | 12.6        | 1.6         | 6.4          | -6.886 | -7.306  | -6.912  | -8.099 | -7.045  | -7.552   | -6.933  |
| Min (detected) | 10.8        | 8.0         | 23.9        | 10.2        | 12.6        | 8.1         | 6.4          | -6.886 | -7.306  | -6.912  | -7.898 | -7.045  | -7.552   | -6.933  |
| <b>Median</b>  | <b>23.1</b> | <b>8.7</b>  | <b>85.0</b> | <b>14.3</b> | <b>18.3</b> | <b>18.4</b> | <b>49.0</b>  | -6.028 | -6.634  | -6.116  | -5.822 | -5.858  | -5.803   | -6.221  |
| Max            | 75.9        | 9.4         | 141.5       | 70.2        | 51.9        | 70.7        | 100.3        | -3.802 | -5.963  | -4.950  | -3.655 | -4.087  | -3.376   | -4.705  |
| Mean           | 27.1        | 8.7         | 83.3        | 20.0        | 22.9        | 21.0        | 52.6         | -5.797 | -6.634  | -6.085  | -6.066 | -5.587  | -5.836   | -5.938  |
| SD             | 20.6        | 1.0         | 37.7        | 17.5        | 14.6        | 17.5        | 36.5         | 0.953  | 0.950   | 0.615   | 1.090  | 1.294   | 1.171    | 0.895   |
| CV%            | 76.0        | 11.4        | 45.2        | 87.5        | 63.4        | 83.7        | 69.4         | 16.4   | 14.3    | 10.1    | 18.0   | 23.2    | 20.1     | 15.1    |
| Detected       | 8/8         | 2/2         | 8/8         | 24/29       | 6/6         | 11/13       | 8/8          | 8/8    | 2/2     | 8/8     | 24/29  | 6/6     | 11/13    | 8/8     |

| OATP2B1        | J 0-2y      | J 2-18y     | J Adult      | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|-------------|-------------|--------------|-------------|-------------|-------------|--------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 20.7        | 21.3        | 23.3         | 20.4        | 30.7        | 7.9         | 7.5          | -6.335 | -6.130  | -7.668  | -6.062 | -5.824  | -6.355   | -7.939  |
| Min (detected) | 20.7        | 21.3        | 23.3         | 20.4        | 30.7        | 7.9         | 7.5          | -6.335 | -6.130  | -7.668  | -6.062 | -5.824  | -6.355   | -7.939  |
| <b>Median</b>  | <b>35.2</b> | <b>31.7</b> | <b>44.8</b>  | <b>37.7</b> | <b>37.0</b> | <b>32.8</b> | <b>29.0</b>  | -5.023 | -4.849  | -7.140  | -4.487 | -4.691  | -4.721   | -6.628  |
| Max            | 64.2        | 42.1        | 62.5         | 96.7        | 62.2        | 67.6        | 43.4         | -4.167 | -3.568  | -5.060  | -1.458 | -2.957  | -2.780   | -4.636  |
| Mean           | 37.1        | 31.7        | 43.2         | 42.1        | 40.7        | 33.7        | 27.3         | -5.179 | -4.849  | -6.924  | -4.472 | -4.623  | -4.766   | -6.540  |
| SD             | 14.2        | 14.7        | 12.5         | 18.1        | 11.3        | 16.6        | 11.6         | 0.767  | 1.812   | 0.819   | 1.091  | 1.074   | 1.317    | 1.010   |
| CV%            | 38.2        | 46.4        | 29.0         | 42.9        | 27.7        | 49.2        | 42.5         | 14.8   | 37.4    | 11.8    | 24.4   | 23.2    | 27.6     | 15.5    |
| Detected       | 8/8         | 2/2         | 8/8          | 29/29       | 6/6         | 13/13       | 8/8          | 8/8    | 2/2     | 8/8     | 29/29  | 6/6     | 13/13    | 8/8     |
| OCT1           | J 0-2y      | J 2-18y     | J Adult      | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 1.2         | 1.2         | 1.2          | 1.2         | 1.2         | 1.2         | 1.2          | -11.21 | -10.33  | -12.75  | -11.03 | -10.73  | -10.97   | -12.48  |
| Min (detected) | 4.7         | 5.8         | 5.1          | 4.3         | 4.6         | 4.6         | 5.1          | -7.926 | -6.417  | -9.893  | -8.731 | -8.732  | -9.733   | -9.082  |
| <b>Median</b>  | <b>7.6</b>  | <b>3.5</b>  | <b>7.7</b>   | <b>4.7</b>  | <b>2.9</b>  | <b>1.2</b>  | <b>3.2</b>   | -7.548 | -8.371  | -9.757  | -7.881 | -8.448  | -8.954   | -8.847  |
| Max            | 11.1        | 5.8         | 15.5         | 23.0        | 21.8        | 9.9         | 12.8         | -6.674 | -6.417  | -8.322  | -5.456 | -4.418  | -6.608   | -6.724  |
| Mean           | 6.7         | 3.5         | 7.2          | 5.7         | 6.0         | 2.5         | 4.9          | -7.968 | -8.371  | -9.914  | -7.977 | -8.294  | -8.874   | -9.516  |
| SD             | 4.0         | 3.3         | 4.8          | 5.6         | 8.0         | 2.7         | 4.5          | 1.554  | 2.764   | 1.469   | 1.641  | 2.309   | 1.454    | 2.054   |
| CV%            | 59.2        | 92.9        | 66.5         | 97.9        | 134.2       | 108.4       | 91.3         | 19.5   | 33.0    | 14.8    | 20.6   | 27.8    | 16.4     | 21.6    |
| Detected       | 6/8         | 1/2         | 6/8          | 16/29       | 3/6         | 3/13        | 4/8          | 6/8    | 1/2     | 6/8     | 16/29  | 3/6     | 3/13     | 4/8     |
| PEPT1          | J 0-2y      | J 2-18y     | J Adult      | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
| Min            | 26.5        | 19.0        | 108.3        | 8.0         | 18.9        | 14.2        | 12.1         | -5.273 | -4.720  | -4.801  | -5.983 | -4.689  | -4.636   | -5.082  |
| Min (detected) | 26.5        | 19.0        | 108.3        | 8.0         | 18.9        | 14.2        | 12.1         | -5.273 | -4.720  | -4.801  | -5.983 | -4.689  | -4.636   | -5.082  |
| <b>Median</b>  | <b>67.5</b> | <b>46.4</b> | <b>230.3</b> | <b>37.2</b> | <b>57.7</b> | <b>39.6</b> | <b>141.9</b> | -4.178 | -4.528  | -4.401  | -4.399 | -4.236  | -4.002   | -4.427  |
| Max            | 175.8       | 73.7        | 387.8        | 106.6       | 117.7       | 213.5       | 356.7        | -3.792 | -4.336  | -4.159  | -2.887 | -3.655  | -2.324   | -3.798  |
| Mean           | 73.8        | 46.4        | 243.9        | 49.1        | 64.7        | 93.2        | 173.0        | -4.336 | -4.528  | -4.478  | -4.437 | -4.249  | -3.785   | -4.455  |
| SD             | 47.6        | 38.7        | 97.8         | 29.5        | 43.6        | 83.3        | 143.0        | 0.496  | 0.271   | 0.244   | 0.653  | 0.383   | 0.720    | 0.383   |
| CV%            | 64.5        | 83.5        | 40.1         | 60.0        | 67.4        | 89.4        | 82.7         | 11.4   | 6.0     | 5.5     | 14.7   | 9.0     | 19.0     | 8.6     |
| Detected       | 8/8         | 2/2         | 8/8          | 29/29       | 6/6         | 13/13       | 8/8          | 8/8    | 2/2     | 8/8     | 29/29  | 6/6     | 13/13    | 8/8     |

| UGT1A1         | J 0-2y      | J 2-18y     | J Adult      | I 0-2y      | I 2-12y     | I 12-18y    | I Adult      | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|-------------|-------------|--------------|-------------|-------------|-------------|--------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 1.8         | 1.8         | 94.8         | 1.8         | 1.8         | 1.8         | 22.6         | -9.390 | -8.148  | -4.746  | -9.619 | -8.046  | -7.630   | -5.219  |
| Min (detected) | 8.5         | 137.1       | 94.8         | 4.1         | 29.8        | 3.7         | 22.6         | -7.224 | -3.440  | -4.746  | -7.447 | -6.038  | -7.630   | -5.219  |
| <b>Median</b>  | <b>17.3</b> | <b>69.5</b> | <b>460.4</b> | <b>10.6</b> | <b>38.2</b> | <b>21.6</b> | <b>120.2</b> | -6.153 | -5.794  | -3.652  | -6.713 | -4.823  | -5.162   | -4.483  |
| Max            | 75.8        | 137.1       | 1045.0       | 146.7       | 88.1        | 222.5       | 465.3        | -5.177 | -3.440  | -2.574  | -4.088 | -2.931  | -3.978   | -3.272  |
| Mean           | 22.2        | 69.5        | 504.3        | 16.9        | 41.9        | 45.4        | 165.9        | -6.717 | -5.794  | -3.750  | -6.740 | -5.191  | -5.249   | -4.408  |
| SD             | 24.0        | 95.7        | 353.6        | 27.8        | 28.8        | 61.0        | 162.2        | 1.573  | 3.329   | 0.684   | 1.389  | 1.718   | 0.922    | 0.635   |
| CV%            | 108.1       | 137.8       | 70.1         | 164.2       | 68.8        | 134.3       | 97.8         | 23.4   | 57.5    | 18.2    | 20.6   | 33.1    | 17.6     | 14.4    |
| Detected       | 6/8         | 1/2         | 8/8          | 20/29       | 5/6         | 12/13       | 8/8          | 6/8    | 1/2     | 8/8     | 20/29  | 5/6     | 12/13    | 8/8     |

| UGT1A10        | J 0-2y     | J 2-18y    | J Adult     | I 0-2y     | I 2-12y     | I 12-18y   | I Adult     | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|------------|------------|-------------|------------|-------------|------------|-------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 3.3        | 3.3        | 3.3         | 3.3        | 3.3         | 3.3        | 3.3         | -9.695 | -8.813  | -9.299  | -9.567 | -7.218  | -9.941   | -7.642  |
| Min (detected) | 13.6       | -          | 23.0        | 6.6        | 13.1        | 10.3       | 12.9        | -6.406 | -       | -6.968  | -7.920 | -7.218  | -8.581   | -7.642  |
| <b>Median</b>  | <b>3.3</b> | <b>3.3</b> | <b>64.8</b> | <b>3.3</b> | <b>17.2</b> | <b>3.3</b> | <b>46.7</b> | -8.018 | -8.025  | -6.509  | -7.779 | -6.595  | -7.441   | -6.342  |
| Max            | 28.4       | 3.3        | 147.0       | 35.4       | 24.0        | 39.3       | 116.0       | -5.772 | -7.237  | -5.897  | -1.483 | -5.249  | -1.768   | -3.348  |
| Mean           | 9.1        | 3.3        | 64.4        | 8.9        | 14.6        | 15.5       | 52.3        | -7.665 | -8.025  | -6.840  | -7.147 | -6.484  | -6.526   | -6.031  |
| SD             | 9.2        | 0.0        | 44.6        | 9.0        | 9.6         | 15.4       | 40.3        | 1.360  | 1.114   | 1.046   | 1.982  | 0.729   | 2.924    | 1.433   |
| CV%            | 100.6      | 0.0        | 69.3        | 100.6      | 65.4        | 99.0       | 77.1        | 17.8   | 13.9    | 15.3    | 27.7   | 11.2    | 44.8     | 23.8    |
| Detected       | 3/8        | 0/2        | 7/8         | 12/29      | 4/6         | 6/13       | 7/8         | 3/8    | 0/2     | 7/8     | 12/29  | 4/6     | 6/13     | 7/8     |

| UGT2B7         | J 0-2y      | J 2-18y     | J Adult      | I 0-2y      | I 2-12y     | I 12-18y    | I Adult     | J 0-2y | J 2-18y | J Adult | I 0-2y | I 2-12y | I 12-18y | I Adult |
|----------------|-------------|-------------|--------------|-------------|-------------|-------------|-------------|--------|---------|---------|--------|---------|----------|---------|
| Min            | 21.3        | 11.2        | 27.1         | 0.9         | 8.5         | 0.9         | 9.7         | -5.762 | -5.475  | -6.267  | -8.512 | -6.154  | -7.237   | -7.029  |
| Min (detected) | 21.3        | 11.2        | 27.1         | 4.9         | 8.5         | 4.0         | 9.7         | -5.762 | -5.475  | -6.267  | -6.837 | -6.154  | -7.237   | -7.029  |
| <b>Median</b>  | <b>39.7</b> | <b>72.3</b> | <b>371.9</b> | <b>31.8</b> | <b>28.8</b> | <b>21.6</b> | <b>29.6</b> | -4.868 | -4.477  | -3.954  | -4.668 | -5.362  | -5.666   | -5.758  |
| Max            | 128.8       | 133.4       | 545.0        | 438.7       | 53.5        | 108.9       | 545.5       | -3.197 | -3.480  | -3.839  | -0.259 | -4.315  | -4.243   | -3.603  |
| Mean           | 55.9        | 72.3        | 335.7        | 60.4        | 29.7        | 28.8        | 111.6       | -4.760 | -4.477  | -4.379  | -4.838 | -5.321  | -5.654   | -5.599  |
| SD             | 38.4        | 86.4        | 191.9        | 85.5        | 18.0        | 31.2        | 182.1       | 0.960  | 1.411   | 0.895   | 1.398  | 0.596   | 0.888    | 1.104   |
| CV%            | 68.8        | 119.5       | 57.2         | 141.7       | 60.5        | 108.0       | 163.2       | 20.2   | 31.5    | 20.4    | 28.9   | 11.2    | 15.7     | 19.7    |
| Detected       | 8/8         | 2/2         | 8/8          | 27/29       | 6/6         | 12/13       | 8/8         | 8/8    | 2/2     | 8/8     | 27/29  | 6/6     | 12/13    | 8/8     |



| VIL1           | J 0-2y      | J 2-18y    | J Adult     | I 0-2y      | I 2-12y     | I 12-18y   | I Adult     |
|----------------|-------------|------------|-------------|-------------|-------------|------------|-------------|
| Min            | 696         | 499        | 2084        | 59          | 333         | 113        | 332         |
| Min (detected) | 696         | 499        | 2084        | 59          | 333         | 113        | 332         |
| <b>Median</b>  | <b>1187</b> | <b>994</b> | <b>5534</b> | <b>1080</b> | <b>1249</b> | <b>931</b> | <b>3063</b> |
| Max            | 2743        | 1489       | 8757        | 2510        | 1971        | 3944       | 6933        |
| Mean           | 1356        | 994        | 5550        | 1153        | 1204        | 1416       | 3354        |
| SD             | 609         | 700        | 2363        | 735         | 733         | 1276       | 2485        |
| CV%            | 44.9        | 70.4       | 42.6        | 63.8        | 60.9        | 90.1       | 74.1        |
| Detected       | 8/8         | 2/2        | 8/8         | 29/29       | 6/6         | 13/13      | 8/8         |

Supplemental table 3. Detailed age group statistics with BLQ values